



EIGHTH EDITION

# HUMAN GENETICS

*Concepts and Applications*

RICKI LEWIS



# Human Genetics

## Concepts and Applications

Eighth Edition

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## HUMAN GENETICS, EIGHTH EDITION

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# About the Author




Ricki Lewis has built a multifaceted career around communicating the excitement of life science, especially genetics and biotechnology. She earned her Ph.D. in genetics in 1980 from Indiana University, working with homeotic mutations in *Drosophila melanogaster*.

Ricki is the original author of *Life*, an introductory biology text; co-author of two human anatomy and physiology textbooks; and author of *Discovery: Windows on the Life Sciences*, an essay collection. She writes and speaks frequently on research and news in genetics, biotechnology, and neuroscience and blogs at [blog.bioethics.net](http://blog.bioethics.net). Since 1980, Ricki has published widely, including one of the first stories on DNA profiling, in *Discover* magazine. She has taught a variety of life science courses at Miami University, the University at Albany, Empire State College, and community colleges. She has also written a novel about stem cells, genetic disease, and iPods.

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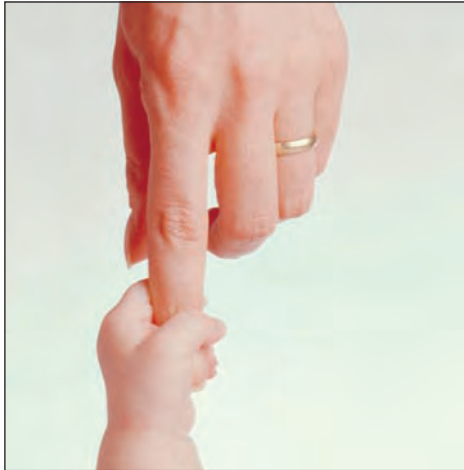


Dedicated to  
Benzena Tucker  
and Glenn Nichols,  
who taught me the  
value of optimism.

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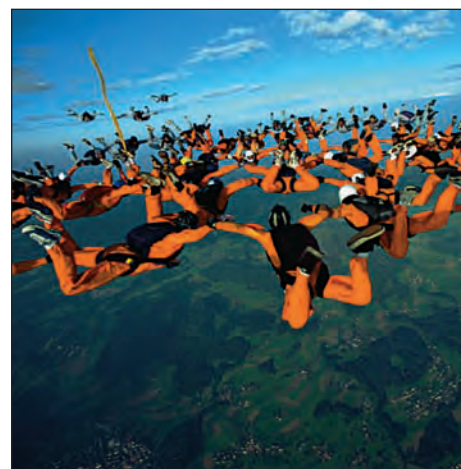
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IN THEIR OWN WORDS



BIOETHICS



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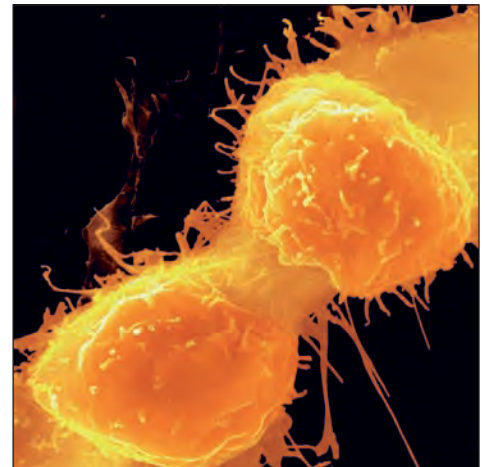
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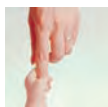
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# Preface

## A New View of Genetics

Headlines at the turn of the millennium heralded the coming completion of the sequencing of the human genome as if, suddenly, we would truly know ourselves. While the ability to match inherited traits and disorders to precise sequences of A, T, C, and G has indeed streamlined research, at the same time we are discovering that there is not “a” human genome at all, but rather many variations of our genetic blueprints. At the same time, we’ve learned that these blueprints are more intricate than expected. When researchers delved into a sample one percent of the genome to probe its complexity, they found that instead of discrete units of information, a genome acts more like hyperlinked text, with parts interacting in tissue and time.

Instead of being the end of a quest, sequencing the human genome was a beginning. Just as a story is more than a sequence of letters, the person represented by a genome is so much more, molded by outside forces as well as by the dynamic genetic instruction manual reiterated in each cell.

While we can’t yet sequence our genomes as easily as we can check blood pressure or cholesterol level, the Internet has brought genetics—in the form of information as well as tests—to consumers. Yet the media, government leaders, and other influential individuals often misunderstand how genes work. The availability of so much information, and the dissemination of so much misinformation, makes it imperative that every citizen has a working knowledge of genetics.

## What Sets This Book Apart

### A Personal Touch

Human genetics is about people, and their voices echo throughout these pages. As a

backdrop to the clear presentation of concepts and facts are the compelling stories of a young fashion magazine editor keeping her leukemia at bay with a drug developed through genetic research (chapter 18); children who are alive today thanks to gene therapy (chapter 20); a man freed from a 25-year prison term following reconsideration of DNA evidence (chapter 14); and even how “peoples of the past” might have lived (chapter 16). The first and final chapters leave the reader to ponder, “Would you want your genome sequenced, and if so, how would you use the information?” Hopefully the book will provide perspective with which to frame an answer.

## Pedagogical Tools

Pedagogical aids help students identify and master basic concepts as well as apply them to a variety of real-life situations. Chapters open with an outline and a “vignette” that is typically a case study. Chapters close with “**A Second Look**,” which are questions about the opening case study, but after chapter concepts are mastered. Within the narrative, at the end of each major section, **Key Concepts** summarize and reinforce core material. The chapters are liberally sprinkled with summary tables, mini-glossaries, and summary figures that are excellent review aids. Where applicable, **Technology Timelines** provide recent historical backdrops, which are useful in interpreting “breakthrough” media reports.

Each chapter ends with a point-by-point **Chapter Summary**, followed by many questions. **Review Questions** measure content knowledge and **Applied Questions** provide practice in using that knowledge. The Applied Questions include **Web Activities** that encourage students to use the latest tools and databases in genetic analysis, and **Cases and Research Results**, which are often taken from headlines, journals, and even fiction.

## Dynamic Art

In genetics as in many areas, a picture is often worth thousands of words. For the more difficult chapters, figures introduce complex mechanisms in steps. In chapter 10, “*Gene Action: From DNA to Protein*,” DNA, RNA, and protein are color-coded, and an icon (that bears an uncanny and unintentional resemblance to an iPod.) identifies and orients each stage in protein production, through several figures. Similarly, in a series of figures in chapter 15, “*Changing Allele Frequencies*,” colored shapes represent individuals, demonstrating the effects on population structure of nonrandom mating, migration, genetic drift, mutation, and natural selection. All of these forces unite in a summary figure and table. The last four chapters synthesize concepts from previous chapters as they introduce genetic technologies.

## Changes to this Edition

### Focus on Concepts

Learning genetics should be about concepts and explanations, not jargon and acronyms. To this end, boldfacing and glossary terms have been chosen with care—if a term isn’t directly related to genetics, or is a disorder name, it isn’t emphasized for memorization. Pronunciations are included in the glossary for all technical terms. Disorders are identified by their Online Mendelian Inheritance in Man (OMIM) number, and the websites on the inside covers direct students to sources of further information.

### New Problems, Cases, and Research Questions

The greatest challenge in revising this book is to choose the clearest examples. Rather than slow the narrative with too many, new examples are often end-of-chapter

questions. In this edition more than 175 new questions review and apply chapter concepts. Answers to all questions are at the back of the book.

## Chapter-By-Chapter

New and updated information is integrated throughout the chapters, and a few features from past editions have been moved.

### Chapter 1 *Overview of Genetics*

- The story of roommates taking genetic tests is a Bioethics box at the chapter's end.
- The Population Biobanks Bioethics box is moved to chapter 14.
- New: Metagenomics considers the body as an ecosystem.
- Overall the chapter is shorter.

### Chapter 5 *Beyond Mendel's Laws*

- New: The porphyrias illustrate and integrate chapter concepts.

### Chapter 6 *Matters of Sex*

- New: Sex ratio and “missing females.”
- Reading on fragile X syndrome features newly discovered symptoms in grandfathers.

### Chapter 7 *Multifactorial Traits*

- Updates on race-based medicine and SNP analysis.
- Emphasis on gene-environment interactions.

### Chapter 8 *Genetics of Behavior*

- Autism update.
- Addiction update.

### Chapter 12 *Gene Mutation*

- Distinguishing polymorphism and mutation.
- New: Copy number variants.
- New: Reverence for dwarfs in ancient Egypt sets an example.

### Chapter 13 *Chromosomes*

- Cases (from past editions and new) begin sections.
- New: Amniocentesis is safer than thought—repercussions.

- New: Chromosomal causes of mental retardation.

### Chapter 14 *Constant Allele Frequencies*

- Update on DNA profiling, including mass disasters.

### Chapter 15 *Changing Allele Frequencies*

- New: The influence of positive selection.
- Most balanced polymorphism examples moved to new table.
- New: Chapter Review table.

### Chapter 16 *Human Ancestry and Eugenics*

- “Peoples of the Past” stories begin key sections.
- Neanderthal update.

### Chapter 17 *Genetics of Immunity*

- New section and figure on antibody diversity.

### Chapter 18 *The Genetics of Cancer*

- Update on pancreatic cancer gene.
- Update on angiogenesis inhibitors.
- New: “Erin's Story: How Gleevec Treats Leukemia.”

### Chapter 20 *Genetic Testing and Treatment*

- Reorganization emphasizes testing and de-emphasizes gene therapy.
- New: Direct-to-consumer genetic testing.
- New: Enzyme replacement therapy.

### Chapter 22 *Genomics*

- New: Major findings of the ENCODE project on the structure and function of a sample one percent of the human genome.

This book continually evolves thanks to input from instructors and students. Please let me know your thoughts and suggestions for improvement (ralewis@nycap.rr.com). The following information is based on the reviews that molded this edition, and my opinion.

## Teaching and Learning Supplements

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21 (*Reproductive Technologies*)

6 (*The Y Wars*)

20 (*Gene Therapy for Canavan Disease*)

10 (*Gene Action: From DNA to Protein*)

14 (*When Allele Frequencies Stay Constant*)

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## Instructor's Manual

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## For the Student

### Genetics: From Genes to Genomes CD-ROM

This easy-to-use CD covers the most challenging concepts in the course and makes them more understandable through presentation of full-color animations and interactive exercises.

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- Self-quizzes to help you master material in each chapter
- Flash cards to ease learning of new vocabulary
- Case studies to practice application of your knowledge of human genetics
- Links to resource articles, popular press coverage, and support groups
- Answers to End-of-Chapter Questions

### Case Workbook to accompany *Human Genetics*, Seventh edition, by Ricki Lewis

This workbook supports the concepts presented in *Human Genetics* through real cases adapted from the author's experience as a genetic counselor, recent scientific and medical journals, interviews, and meetings. The workbook provides practice for constructing and interpreting pedigrees; applying Mendel's laws; reviewing the relationships of DNA, RNA, and proteins; analyzing the effects of mutations; evaluating phenomena that distort Mendelian ratios; designing gene therapies; and applying new genomic approaches to understanding inherited disease. A special set of exercises at the end of the workbook links concepts across chapters. An answer key is available for the instructor.

## Acknowledgements

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I also thank my wonderful family: Larry, daughters Heather, Sarah, and Carly, and our legion of felines.

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# Visual Preview

## Instructional Art Program

Art program puts molecular and cellular information into a familiar context.

Figures of complex processes focus on essentials and are presented in easy-to-follow steps

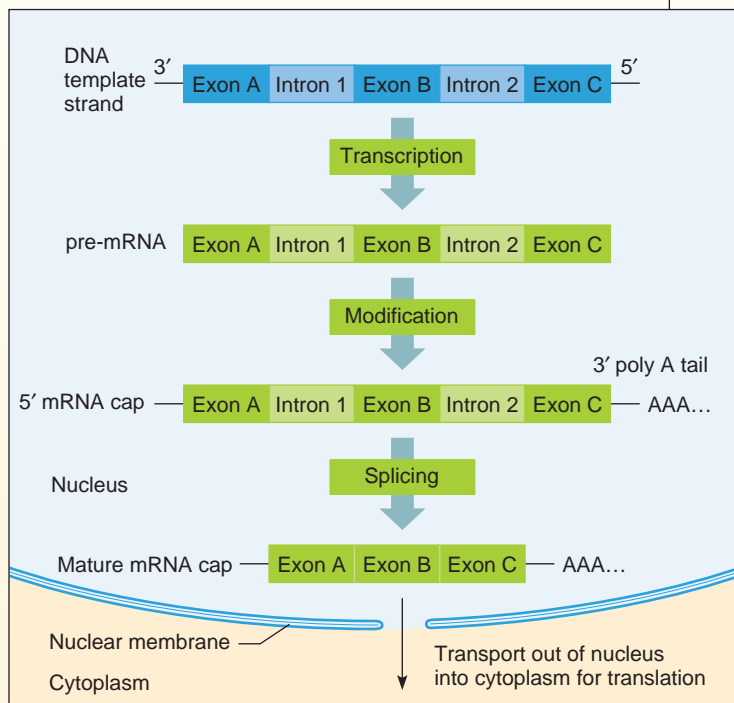


Figure 10.10

Comparative figures provide clarity and aid understanding

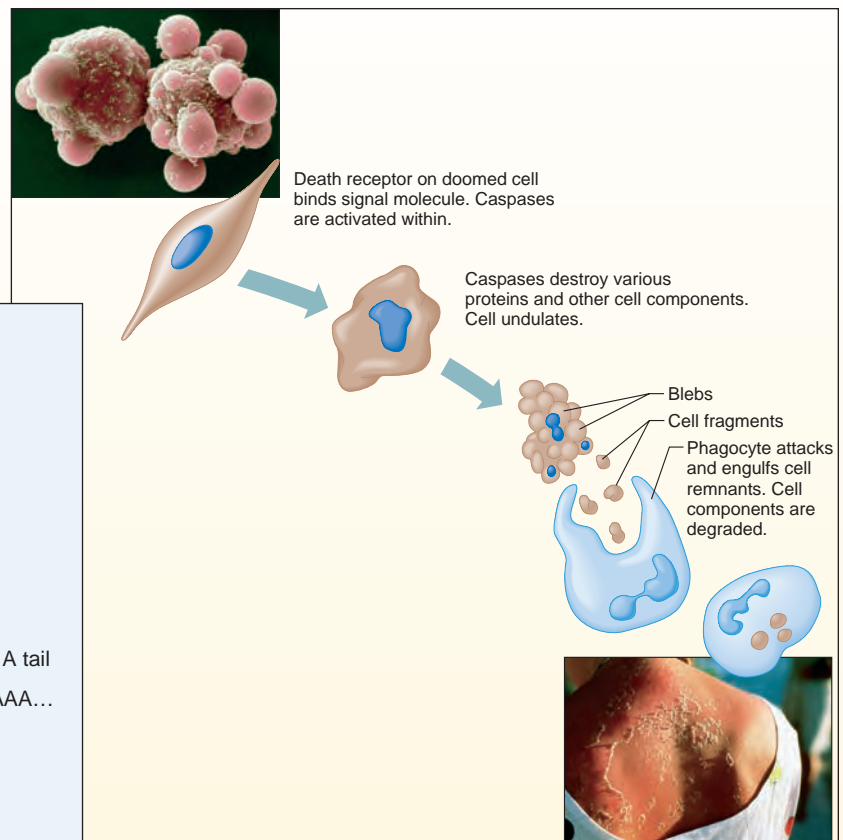


Figure 2.18

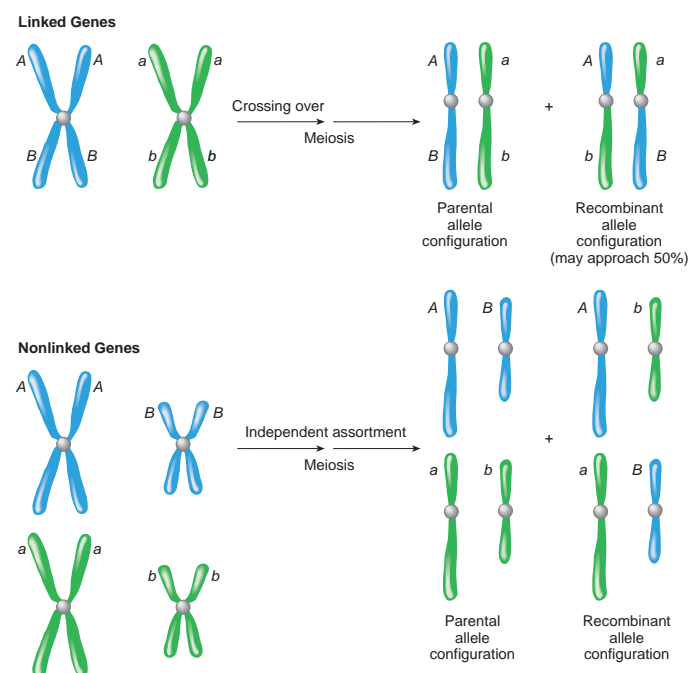


Figure 5.14



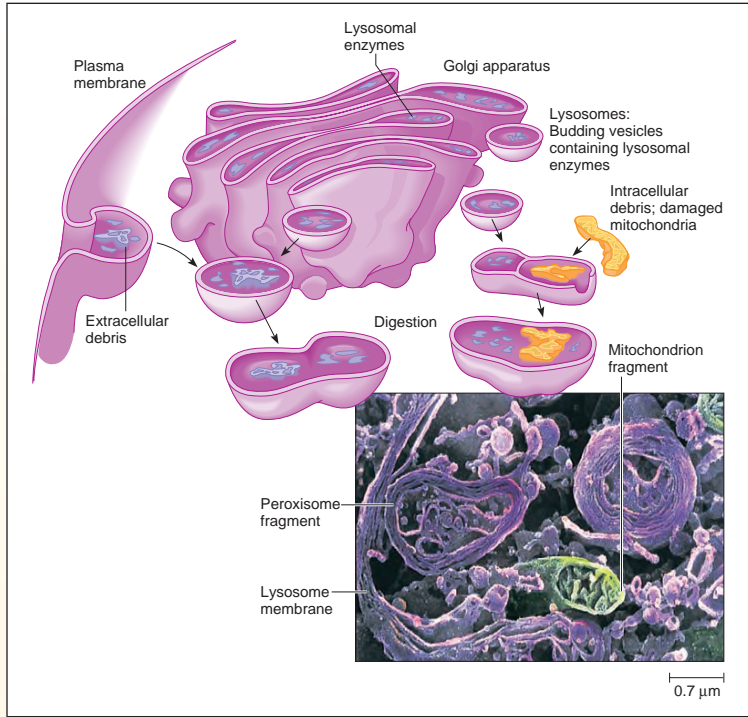


Figure 2.6

Photographs bring illustrations to life

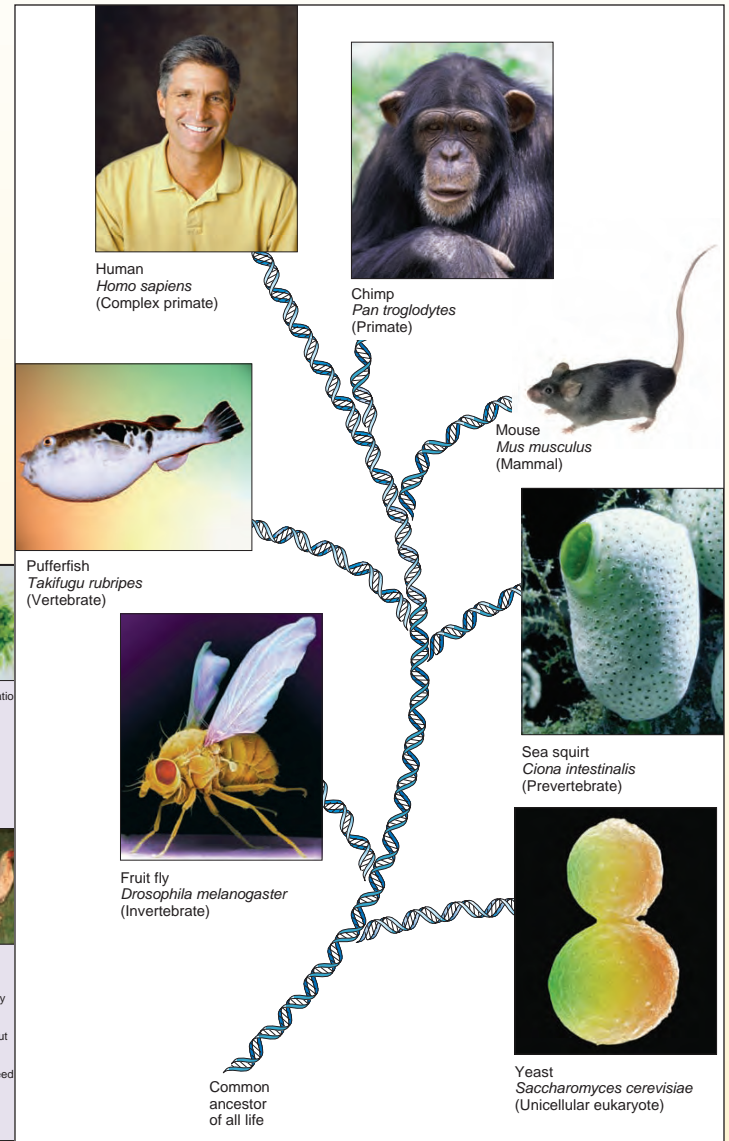


Figure 1.4

Figures covering comparative genomics help to place humans in a broader, evolutionary context.

<b>Bacterium</b> ( <i>Dehalococcoides ethenogenes</i> ) ~1.5 million bases ■ Bioremediation: Dechlorinates water pollutants ■ Biotechnology: Transfer 19 dechlorinating enzymes a.		<b>Protozoan</b> ( <i>Cryptosporidium parvum</i> ) ~9.1 million bases ■ Human pathogen: Diarrheal illness, severe in immunosuppressed ■ Lacks 2 organelles ■ Difficult to culture in lab because of unusual metabolism ■ Lives in city water supplies b.		<b>Moss</b> ( <i>Physcomitrella patens</i> ) ~500 million bases ■ Biotechnology: genes provide dehydration resistance. Transfer? ■ Genome easy to manipulate ■ Evolution: first land plants c.	
<b>Honey Bee</b> ( <i>Apis mellifera</i> ) ~300 million bases ■ Agriculture: honey ■ Animal societies ■ Compare to other insect genomes ■ Ecology: Compare to Africanized bees in southwestern U.S. d.		<b>Coelacanth</b> ( <i>Latimeria menadoensis</i> ) ~1.7 billion bases ■ Evolution: "living fossil" unchanged from ancestor that preceded land tetrapods ■ Thought extinct until 1938 discovery near South Africa ■ Genome easier to study than other fishes because few repeats e.		<b>Red jungle fowl</b> ( <i>Gallus gallus</i> ) ~1 billion bases ■ Evolution: Dinosaur descendant; conserved control sequences ■ Good model organism. Can study early development in eggs, and aging ■ Same number of genes as humans, but genome 1/3 the size ■ Agriculture: Identify genes that limit need drugs in feed ■ Medicine: Carries avian flu virus f.	
<b>Tammar wallaby</b> ( <i>Macropus eugenii</i> ) ~3.6 billion bases ■ Evolution: Marsupials (pouched mammals split from placental mammals ~130 millions years ago) ■ Perpetually pregnant: give birth on same day each year ■ 1 million on Kangaroo Island, Australia g.		<b>Hereford cow</b> ( <i>Bos taurus</i> ) ~3 billion bases ■ Medicine: Transmission of prion disorder (BSE) ■ Agriculture: Improved meat and milk production; disease prevention ■ Study genetic variability in different breeds h.		<b>Dog</b> ( <i>Canis familiaris</i> ) ~2.5 billion bases ■ Evolution: Extreme artificial selection created 300+ breeds; compare 10 breeds, wolves, coyote ■ 400+ diseases from founder effect and inbreeding ■ Medicine: Diseases occur in humans, too (rheumatoid arthritis, cancers, heart and eye disorders, deafness) ■ Biotechnology: Pioneered diabetes treatment and bone marrow transplant i.	

Figure 22.8

## Extraordinary Learning Aids

Pedagogical aids ensure that students can identify the basic concepts presented and exemplified in each chapter.

- **Chapter outline** previews contents.
- **Chapter opening case study** provides a real-life story related to the chapter concepts.
- **A Second Look** returns to the chapter opening story to test mastery of concepts.
- **Key concepts** are summarized to reinforce major concepts and core material.
- **Chapter summaries** review the major concepts and highlight the most important vocabulary.
- **Review questions** assess content knowledge.
- **Applied questions** guide students in solving challenges that genetic information presents.
- **Answers** to all questions are available at [www.mhhe.com/Lewisgenetics8](http://www.mhhe.com/Lewisgenetics8).

## Multifactorial Traits

### CHAPTER CONTENTS

- 7.1 Genes and the Environment Mold Most Traits
  - Polygenic Traits Are Continuously Varying
  - Fingerprint Patterns
  - Height
  - Eye Color
  - Skin Color
- 7.2 Investigating Multifactorial Traits
  - Empiric Risk
  - Heritability
  - Adopted Individuals
  - Twins
  - Association Studies
- 7.3 Two Multifactorial Traits
  - Heart Health
  - Weight

### CLEFT LIP AND PALATE

The young couple was shocked when they first saw their daughter. She had a cleft lip and palate—a hole between her nose and upper lip. The parents soon discovered that feeding Emily was difficult, because she could not maintain suction. Special nipples on her bottles helped.

Today, Emily is 14, and has a glorious smile. The defect occurred between weeks 4 and 12 of prenatal development, when her nose and jaw failed to meet and close. Emily had several surgeries. Her first procedure, at 4 months, repaired her lip; the second, at a year, connected the edges of her palate (the roof of the mouth) and repositioned tissue at the back of her throat to correct her nasal speech. A speech and language therapist helped with Emily's early feeding problems and assisted her when frequent ear infections, due to openings at the back of her throat, caused hearing loss. At age seven Emily had orthodontia to make room for her permanent teeth, and at age 10, bone from her hip was used to strengthen her palate so that it could support teeth. At age 16, Emily can have surgery on her nose to build it up and straighten it.

Cleft lip, with or without cleft palate, is very variable in severity and has genetic and environmental components. Known causes include prenatal exposure to certain drugs used to treat seizures, anxiety, and high cholesterol; pesticide residues; cigarette smoke; and infections. Emily's parents were nervous



Cleft lip is more likely to occur in a person who has a relative with the condition. The child has had corrective surgery.

## A Second Look

1. How did natural selection mold the differing abilities of people to digest milk in different populations?
2. Ability to digest milk arose from positive selection. Cite an example of negative selection. (You can invent one.)
3. How can lactose intolerance be the wild type phenotype in a population?
4. Explain how geography played a role in the evolution of genes that enable people to digest cow's milk.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

3-methyl glutathione aciduria type III  
Jewish genius?

Table 15.6  
Chapter Review

Mechanism of Allele Frequency Change	Examples
Nonrandom mating	Agriculture Cape population and Arnold Hopi Indians with albinism Genghis Khan's Y chromosome Rape in Darfur Consanguinity Galactokinase deficiency in Europe ABO blood type distribution Clines along the Nile and in Italy
Migration	
Genetic drift	
Founder effect	Fumarate deficiency in Arizona/Utah BRCA1 breast cancer in French Canadians Dunkers Old Order Amish and Mennonites Africans and porphyria variegata Pituitary blindness Chetals Chernobyl massacre Chapters 12 and 13 Lactose intolerance TB incidence and virulence HIV infection Antibiotic resistance Sickle cell disease and malaria Prion disease and cannibalism CF and diarrheal disease
Population bottleneck	
Mutation	
Natural selection	

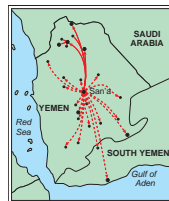


Figure 15.14 The origin of PKU. deletion in Israeli Yemenite Jews probably arose in San'a, Yemen, in the mid-eighteenth century. The allele spread northward as families moved from San'a in 1809 (solid arrows) and subsequent spread to other regions (broken arrow). Source: Data from Smadar Avigad, et al., 'A single origin of phenylketonuria in Yemenite Jews', Nature 364:170, March 8, 1990.

### Key Concepts

1. PKU originated more than once.
2. Genetic drift, balanced polymorphism, and perhaps mutation have affected its prevalence.

## Summary

### 15.1 Nonrandom Mating

1. Hardy-Weinberg equilibrium assumes all individuals mate with the same frequency and choose mates without regard to phenotype. This rarely happens. We choose mates based on certain characteristics, and some people have many more children than others.
2. DNA sequences that do not cause a phenotype important in mate selection or reproduction may be in Hardy-Weinberg equilibrium.
3. Consanguinity increases the proportion of homozygotes in a population, which may

lead to increased incidence of recessive illnesses or traits.

### 15.2 Migration

4. Clines are changes in allele frequencies from one area to another.
5. Clines may reflect geographical barriers or linguistic differences and may be either abrupt or gradual.
6. Human migration patterns through history explain many cline boundaries. Forces behind migration include escape from persecution and a nomadic lifestyle.

### 15.3 Genetic Drift

7. Genetic drift occurs when a small population separates from a larger one and or its members breed only among themselves, perpetuating allele frequency not characteristic of the larger population due to chance sampling.
8. A founder effect occurs when a few individuals found a settlement and the alleles form a new gene pool, amplifying their alleles and eliminating others.
9. A population bottleneck is a narrowing of genetic diversity that occurs after members of a population die and the survivors rebuild the gene pool.

### 15.4 Mutation

10. Mutation continually introduces new alleles into populations. It occurs as a consequence of DNA replication errors.
11. Mutation does not have as great an influence on disrupting Hardy-Weinberg equilibrium as the other factors.
12. The genetic load is the collection of deleterious alleles in a population.

### 15.5 Natural Selection

13. Environmental conditions influence allele frequencies via natural selection. Alleles that do not enable an individual to reproduce in a particular environment are selected against and diminish in the population, unless conditions change. Beneficial alleles are retained.
14. In balanced polymorphism, the frequencies of some deleterious alleles are maintained

when heterozygotes have a reproductive advantage under certain conditions.

### 15.6 Putting It All Together: PKU Revisited

15. Frequencies of different mutations in different populations provide information on the natural history of alleles and on the relative importance of nonrandom mating, genetic drift, and natural selection in deviations from Hardy-Weinberg equilibrium.

## Review Questions

1. Give examples of how each of the following can alter allele frequencies from Hardy-Weinberg equilibrium:
  - a. nonrandom mating
  - b. migration
  - c. a population bottleneck
  - d. mutation
2. Explain the influence of natural selection on:
  - a. the virulence of tuberculosis.
  - b. bacterial resistance to antibiotics.
  - c. the changing degree of genetic diversity in an HIV population during infection.
3. Why can increasing homozygosity in a population be detrimental?
4. How might a mutant allele that causes an inherited illness in homozygotes persist in a population?
5. Give an example of an inherited disease allele that protects against an infectious illness.
6. Explain how table 15.2 indicates that genetic drift has occurred among the Dunkers.
7. How does a founder effect differ from a population bottleneck?
8. Describe two scenarios in human populations, one of which accounts for a gradual cline, and one for an abrupt cline.
9. How do genetic drift, nonrandom mating, and natural selection interact?
10. Define:
  - a. founder effect
  - b. balanced polymorphism
  - c. genetic load
11. How does a knowledge of history, sociology, and anthropology help geneticists to interpret allele frequency data?

## Applied Questions

1. Begin with the original population represented at the center of Figure 15.13, and deduce the overall, final effect of the following changes:
  - Two yellow square individuals join the population when they stop by on a trip and stay awhile.
  - Four red circle individuals are asked to leave as punishment for criminal behavior.
  - A blue triangle man has sex with many females, adding five blue triangles to the next generation.
  - A green diamond female produces an oocyte with a mutation that results in adding a yellow square to the next generation.
  - A new infectious disease affects only blue triangles and yellow squares, removing two of each from the next generation.
2. Before 1500 A.D., medieval Gaelic society in Ireland isolated itself from the rest of Europe, physically as well as culturally. Men in the group are called "descendants of Niall" and they all share a Y chromosome inherited from a single shared ancestor. In the society, men took several partners, and sons born out of wedlock were fully accepted. One male, for example, Lord Turlogh O'Donnell, had 10 wives and concubines, who gave him 18 sons and 59 grandsons. Today, in a corner of northwest Ireland, 1 in 5 men has the "descendant of Niall" Y chromosome. In all of Ireland, the percentage of Y chromosomes with the Niall signature is 8.2 percent. In western Scotland, where the Celtic language is similar to Gaelic, 7.3 percent of the males have the telltale Niall Y. In the U.S., among those of European descent, it is 0.2 percent. Worldwide, the Niall Y chromosome makes up only 0.13 percent of the total. What concept from the chapter do the data illustrate?
3. Fred Schnee, who teaches human genetics at Loras College in Iowa, offers a good example of genetic drift: seven castaways are shipwrecked on an island. The first mate has blue eyes, the others brown. A coconut falls on the first mate, killing him. The coconut accident is a chance event affecting a small population. Explain how this event would affect allele frequency, and offer another example of genetic drift.
4. The Old Order Amish of Lancaster, Pennsylvania have more cases of polydactyly (extra fingers and toes) than the rest of the world combined. All of the affected individuals descend from the same person, in whom the dominant mutation originated. Does this illustrate a population bottleneck, a founder effect, or natural selection? Give a reason for your answer.
5. Predict how natural selection might affect the frequency of alleles that protect against



## Reading 7.1

### Solving a Problem: Connecting Cousins

With more genetic tests becoming available as the human genome sequence is analyzed, more people are learning that relatives beyond their immediate families have certain gene variants that might affect their health. Because the genetic closeness of the relationship impacts the risk of developing certain conditions, it is helpful to calculate the percentage of the genome that two relatives share.

The pedigree in figure 1 displays an extended family, with "YOU" as the starting point. Calculate the percent of the genome shared for your first cousins once and twice removed (that is, removed from you by one or two generations, respectively)—in the figure, in generations III and II, while YOU are in generation IV. A second, third, or fourth cousin, by contrast, is in the same generation on a pedigree as the individual in question; see, for example, individual V-1 in figure 1. Table 1 summarizes the genetic relationships between cousins.

#### SOLUTION

The rules: Every step between parent and child, or sibling and sibling, has a value of 1/2, because these types of pairs share

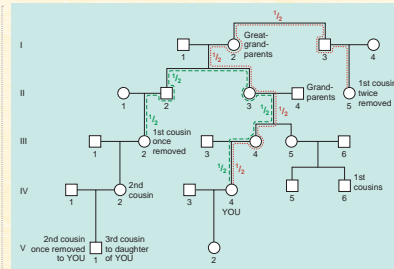


Figure 1 Pedigrees help determine the percentage of the genome two relatives share.

approximately 1/2 of their genes, according to Mendel's first law (chromosome segregation).

Table 7.3 Heritabilities for Some Human Traits

Trait	Heritability
Clubfoot	0.8
Height	0.8
Blood pressure	0.6
Body mass index	0.5
Verbal aptitude	0.7
Mathematical aptitude	0.3
Spelling aptitude	0.5
Total fingerprint ridge count	0.9
Intelligence	0.5–0.8
Total serum cholesterol	0.6

but certain variants much more common in one group due to long-term environmental differences. Populations in equatorial Africa, for example, have darker skin than sun-deprived Scandinavians.

Researchers use several statistical methods to estimate heritability. One way is to compare the actual proportion of pairs of people related in a certain manner who share a particular trait, to the expected proportion of pairs that would share it if it were inherited in a Mendelian fashion. The expected proportion is derived by knowing the blood relationships of the individuals and using a measurement called the **coefficient of relatedness**, which is the proportion of genes that two people related in a certain way share (table 7.4).

A parent and child share 50 percent of their genes, because of the mechanism of meiosis. Siblings share on average 50 percent of their genes, because they have a 50 percent chance of inheriting each allele for a gene from each parent. Genetic counselors use the designations of primary (1<sup>st</sup>), secondary (2<sup>nd</sup>), and tertiary (3<sup>rd</sup>) relatives when calculating risks (table 7.4 and figure 7.6). For extended or complicated pedigrees, the value of 1/2 or 50 percent between siblings and between parent-child pairs can be used to trace and calculate the percentage of genes shared between people related in other ways. Reading 7.1 discusses how to calculate percentages of the genome shared for first cousins separated by generations, described as "removed" by one or more generations.

involved in healing. Analysis on the first day indicated activation of the same suite of genes whose protein products heal injury to the deep layer of skin—a total surprise that suggests new points for drugs to intervene.

### Solving a Problem: Interpreting a DNA Sequence Variation Microarray

The second major type of DNA microarray experiment, a DNA sequence variation analysis, screens mutations, SNPs, and the wild type sequence for a particular gene. Figure 19.10 shows possible patterns for comparing two individuals for a single-gene recessive disorder. Each person's microarray would have two fluorescing spots if he or she is a heterozygote (because there are two different alleles), or just one if he or she is a homozygote.

Interpreting the results of a DNA sequence variation analysis depends upon the specific nature of a disorder. In cystic fibrosis (CF), for example, a person could be homozygous recessive for a mutant allele that confers symptoms so mild that they had been attributed to recurrent respiratory infection. In another scenario, different alleles from two heterozygotes combine to cause severe illness in a child. This is what happened to Monica and Bill in figure 9.11. Routine screening during Monica's pregnancy revealed that she carries the common CF allele ΔF508, which is associated with severe disease. Bill was then tested and found to be a carrier, too, but for the rarer allele G542X. Monica had amniocentesis, and a DNA microarray test of the sampled fetal cells revealed the pattern in figure 19.11c—both mutant alleles. The computer then consulted a database of known allele combinations and predicted a poor prognosis.

DNA sequence variation analysis also uses "SNP chips" that cover selected regions of more than one gene and can identify disease-associated variations over wide swaths of a genome. Such tests might predict whether variants in genes other than the one that causes CF could affect the phenotype of Monica and Bill's child, such

"Solving a Problem" sections appear throughout the book where students can perform a genetic analysis. Each section presents a step-by-step sample computation.

Case studies and Research Results found after each chapter apply, and sometimes extend, concepts. These case studies supplement those in the *Case Workbook to Accompany Human Genetics* by Ricki Lewis.

from nearly all of the 2,188 residents of the Pacific Island of Kosrae, and found that 1,709 of them are part of the same pedigree. The incidence of all of the symptoms of syndrome X is much higher in this population than for other populations. Suggest a reason for this finding, and indicate why it would be difficult to study these particular traits, even in an isolated population.

- By which mechanisms discussed in this chapter do the following situations alter Hardy-Weinberg equilibrium?
  - Ovalocytosis (OMIM 166910) is caused by a beneficial mutation. A protein that anchors the red blood cell plasma membrane to the cytoplasm is abnormal, making the membrane unusually rigid. As a result, the parasites that cause malaria cannot enter the red blood cells of individuals with ovalocytosis.
  - In the mid-1700s, a multicolored male cat from England crossed the sea and settled in Boston, where he left behind quite a legacy of kittens—about half of whom also had six, seven, eight, or even nine digits on their paws. People loved the odd felines and bred them. Today, in Boston and nearby regions, multicolored cats are far more common than in other parts of the United States.
  - Many slaves in the United States arrived in groups from Nigeria, which

is an area in Africa with many ethnic subgroups. They landed at a few sites and settled on widely dispersed plantations. Once emancipated, former slaves in the South were free to travel and disperse.

#### Web Activities

Visit the Online Learning Center (OLC) at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Student Edition**, chapter 15, and **Web Activities** to find the website link needed to complete the following activities.

- Go to the Centers for Disease Control and Prevention website, and the journal *Emerging Infectious Diseases*. Using this resource, describe an infectious disease that is evolving, and cite the evidence for this.
- Do a Google search for a pair of disorders listed in table 15.3 (balanced polymorphism) and discuss how the carrier status of the inherited disease protects against the second condition.
- The human population of India is divided into many castes, and the people follow strict rules governing who can marry whom. Researchers from the University of Utah compared several genes among 265 Indians of different castes and 750 people from Africa, Europe, and Asia. The study found that the genes of higher

Indian castes most closely resembled those of Europeans, and that the genes of the lowest castes most closely resembled those of Asians. In addition, the study found that maternally inherited genes (mitochondrial DNA) more closely resembled Asian versions of those genes, but paternally inherited genes (on the Y chromosome) more closely resembled European DNA sequences. Construct an historical scenario to account for these observations.

- The ability to digest lactose is found in several populations where dairy is part of the diet. This ability is the result of natural selection. What is the significance of the observation that different populations that can digest lactose have different alleles for the lactase gene?
- People who have one or two alleles bearing a nonsense mutation in the *capnase-12* gene are exceptionally resistant to certain severe infections (pneumonia, diarrhea, measles, and malaria). By comparing the gene's sequence in diverse human populations, researchers estimate that the mutation arose in Africa more than 100,000 years ago. At first the mutation remained rare, but by 60,000 years ago, when human populations were more organized and larger, the mutant allele became more common, and continues to increase in prevalence. Explain the role of natural selection in the changing allele frequency.

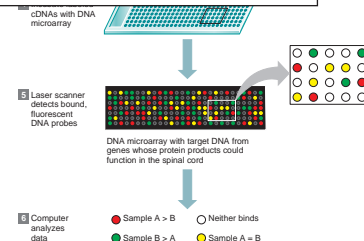


Figure 19.9 A DNA microarray experiment reveals gene expression in response to spinal cord injury.

Web activities encourage students to find information about human genetics that particularly interests them. They also provide an opportunity to find the latest genetic information and to use tools and databases in genetic analysis.

## A Second Look

- How did natural selection mold the differing abilities of people to digest milk in different populations?
- Ability to digest milk arose from positive selection. Cite an example of negative selection. (You can invent one.)
- How can lactose intolerance be the wild type phenotype in a population?
- Explain how geography played a role in the evolution of genes that enable people to digest cow's milk.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook to Accompany Human Genetics*:

- 3-methyl glutaric aciduria type III
- Jewish genius?



Do you need additional review? Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.



# GENETICS RESOURCES

In 1966, Dr. Victor McKusick, a geneticist at Johns Hopkins University, began to publish an annual compendium of known inherited diseases in humans, called Mendelian Inheritance in Man. The heavy volume has evolved into a constantly updated electronic version, searchable at the website for the National Center for Biotechnology Information: [www.ncbi.nlm.nih.gov/](http://www.ncbi.nlm.nih.gov/) The numbered entries are organized as follows:

100,000s = autosomal dominant

200,000s = autosomal recessive

300,000s = X-linked

400,000s = Y-linked

500,000s = mitochondrial

It is helpful to pair OMIM information with descriptions on other websites, including experiences written by families with inherited disease. Below are listed general websites, and on the back inside cover, more specific websites.

## ORGANIZATIONS

Access Excellence

[www.accessexcellence.org](http://www.accessexcellence.org)

American Society of Gene Therapy

[www.asgt.org](http://www.asgt.org)

American Society of Human Genetics

[www.ashg.org](http://www.ashg.org)

American Society of Medical Genetics

[www.acmg.net](http://www.acmg.net)

Bioethics blog

<http://blog.bioethics.net>

Department of Energy

[genomics.energy.gov](http://genomics.energy.gov)

Genetics & Public Policy Center

[www.DNAPolicy.org](http://www.DNAPolicy.org)

Genetics Home Reference

<http://ghr.nlm.nih.gov>

International Society for Stem Cell Research

[www.isscr.org](http://www.isscr.org)

Mendel Museum of Genetics

[www.Mendel-museum.org](http://www.Mendel-museum.org)

National Cancer Institute

[www.cancer.gov](http://www.cancer.gov)

National Center for Biotechnology Information

[www.ncbi.nlm.nih.gov/](http://www.ncbi.nlm.nih.gov/)

National Coalition for Health Professional  
Education in Genetics

[www.nchpeg.org](http://www.nchpeg.org)

National Library of Medicine Medlineplus Database

[medlineplus.gov](http://medlineplus.gov)

National Society of Genetic Counselors

[www.nsgc.org](http://www.nsgc.org)

## FERTILITY

[fertilityjourney.com](http://fertilityjourney.com)

[www.resolve.org](http://www.resolve.org)

Cryo Eggs International

[www.cryoeggsintl.com](http://www.cryoeggsintl.com)

N. W. Andrology & Cryobank

[www.nwcryobank.com](http://www.nwcryobank.com)

National Embryo Donation Center

[www.embryodonation.org/](http://www.embryodonation.org/)

## FORENSICS

Combined DNA Index System

[www.ncjrs.gov/nij/DNAbro/comb.html](http://www.ncjrs.gov/nij/DNAbro/comb.html)

Council for Responsible Genetics

[www.gene-watch.org](http://www.gene-watch.org)

Innocence Project

[www.innocenceproject.org](http://www.innocenceproject.org)

<http://learn.genetics.utah.edu/features/forensics/>

<http://www.dnfiles.org/home.html>

<http://www.genetictechnologies.com>

## RARE DISORDERS

Office of Rare Diseases

<http://rarediseases.info.nih.gov>

[www.familyvillage.wisc.edu/library.htm](http://www.familyvillage.wisc.edu/library.htm)

[orpha.net](http://orpha.net)

[www.geneticalliance.org/](http://www.geneticalliance.org/)

National Organization for Rare Disorders

[www.rarediseases.org](http://www.rarediseases.org)

## DISEASE GROUPS

alopecia areata  
[www.naaf.org](http://www.naaf.org)  
alpha-1 antitrypsin deficiency  
[alphaone.org](http://alphaone.org)  
Canavan disease  
[www.canavan.org](http://www.canavan.org)  
[www.canavandisease.org](http://www.canavandisease.org)  
CHARGE Syndrome Foundation  
<http://www.chargesyndrome.org>  
Chicago Center for Jewish  
Genetic Disorders  
[jewishgeneticscenter.org](http://jewishgeneticscenter.org)  
congenital adrenal hyperplasia  
[www.caresfoundation.org](http://www.caresfoundation.org)  
Cornelia de Lange  
Syndrome Foundation  
[www.CdLSusa.org](http://www.CdLSusa.org)  
Cystic Fibrosis Foundation  
[www.cff.org](http://www.cff.org)  
dwarfism  
Little People of America  
[www.lpaonline.org/](http://www.lpaonline.org/)  
Familial Dysautonomia  
Foundation Inc.  
[www.familialdysautonomia.org](http://www.familialdysautonomia.org)  
Fraxa Research Foundation  
[www.fraxa.org](http://www.fraxa.org)  
Gaucher disease  
National Gaucher Foundation  
[www.gaucherdisease.org](http://www.gaucherdisease.org)  
hemochromatosis  
American Hemochromatosis Society  
[www.americanhs.org/](http://www.americanhs.org/)  
hemophilia  
National Hemophilia Foundation  
[www.hemophilia.org](http://www.hemophilia.org)  
Huntington disease  
HD Society of America  
[www.hdsa.org](http://www.hdsa.org)  
isodicentric 15  
<http://www.idic15.org>  
Jewish Genetic Diseases  
[www.mazornet.com/genetics/  
index.asp](http://www.mazornet.com/genetics/index.asp)

long QT Syndrome  
[www.longqt.org](http://www.longqt.org)  
Lowe Syndrome Association  
[www.lowesyndrome.org](http://www.lowesyndrome.org)  
Maple Syrup Urine Disease  
Family Support Group  
[www.msud-support.org/](http://www.msud-support.org/)  
mucopolysaccharidoses  
[www.mppsociety.org](http://www.mppsociety.org)  
Muscular Dystrophy Association  
[www.mda.org/](http://www.mda.org/)  
ocular albinism  
[www.visionofchildren.org](http://www.visionofchildren.org)  
Osteogenesis Imperfecta Foundation  
[www.oif.org](http://www.oif.org)  
phenylketonuria  
[www.pku.com](http://www.pku.com)  
polycystic kidney disease  
[www.pkdcure.org](http://www.pkdcure.org)  
Porphyria Foundation  
[www.porphyrifoundation.com](http://www.porphyrifoundation.com)  
Prader-Willi Syndrome Association  
<http://www.pwsausa.org>  
Preeclampsia Foundation  
[www.preeclampsia.org](http://www.preeclampsia.org)  
Progeria Research  
[www.progeriaresearch.org](http://www.progeriaresearch.org)  
retinitis pigmentosum  
[www.rpinternational.org](http://www.rpinternational.org)  
Sickle Cell Disease  
Association of America  
[www.sicklecelldisease.org](http://www.sicklecelldisease.org)  
spinal muscular atrophy  
Claire Altman Heine Foundation  
[www.preventsma.org](http://www.preventsma.org)  
Tay-Sachs disease  
Late Onset Tay-Sachs Foundation  
[www.lotsf.org](http://www.lotsf.org)  
trisomies  
[www.livingwithtrisomy13.org](http://www.livingwithtrisomy13.org)  
[www.trisomy18support.org](http://www.trisomy18support.org)  
[www.trisomy21online.com](http://www.trisomy21online.com)  
Wilson's Disease Association  
[www.wilsonsdisease.org](http://www.wilsonsdisease.org)

XO syndrome  
[www.turner-syndrome-us.org/](http://www.turner-syndrome-us.org/)  
XXY syndrome  
[Klinefeltersyndrome.org](http://Klinefeltersyndrome.org)  
xeroderma pigmentosum  
[www.xps.org](http://www.xps.org)

## GENETIC TESTING

Analytical Genetics Technology  
Centre  
[www.analyticalgenetics.ca](http://www.analyticalgenetics.ca)  
Baylor College of Medicine  
Medical Genetics Laboratories  
[www.bcmgeneticlabs.org](http://www.bcmgeneticlabs.org)  
Clinical Molecular Diagnostic  
Laboratory  
[www.cityofhope.org/cmdl](http://www.cityofhope.org/cmdl)  
Consumer Genetics  
[www.consumergenetics.com](http://www.consumergenetics.com)  
DNA Direct  
[www.dnadirect.com](http://www.dnadirect.com)  
Emory Genetics Laboratory  
[www.genetics.emory.edu](http://www.genetics.emory.edu)  
Gene Dx  
[www.genedx.com](http://www.genedx.com)  
Genelex  
[www.genelex.com](http://www.genelex.com)  
GeneTree DNA Testing Center  
[www.genetree.com](http://www.genetree.com)  
Genzyme Genetics  
[www.genzymegenetics.com](http://www.genzymegenetics.com)  
Myriad Genetics  
[www.myriad.com](http://www.myriad.com)  
National Newborn Screening  
and Genetics Resource Center  
<http://genes-r-us.uthscsa.edu>  
Relative Genetics  
[www.relativegenetics.com](http://www.relativegenetics.com)  
Sequenom  
[www.sequenom.com](http://www.sequenom.com)  
Sorenson Genomics  
[www.sorensongenomics.com](http://www.sorensongenomics.com)  
University of Chicago Genetic  
Services Laboratory  
[www.genes.uchicago.edu](http://www.genes.uchicago.edu)





# Overview of Genetics

## CHAPTER CONTENTS

- 1.1 **Levels of Genetics**
  - DNA
  - Genes, Chromosomes, and Genomes
  - Cells, Tissues, and Organs
  - Individual
  - Family
  - Population
  - Evolution
- 1.2 **Most Genes Do Not Function Alone**
  - Genes and Disease Risk
  - Genetic Determinism
- 1.3 **Applications of Genetics**
  - Establishing Identity and Ancestry
  - Health Care
  - Agriculture
  - Ecology
  - A Global Perspective

## SUPERBOY

The German boy appeared different from birth—his prominent arm and thigh muscles suggested he'd been lifting weights while in the womb. By five years of age, his muscles twice normal size, he could lift heavier weights than many adults. He also had half the normal amount of body fat. Relatives share the trait. The boy's mother was a professional sprinter and is unusually strong, as are three close male relatives. One is a construction worker who regularly and effortlessly lifts very heavy stones.

Genes from both parents caused the boy's unusual body composition. His cells cannot produce a protein called myostatin, which normally stops stem cells from making a muscle too large. A mutation turns off this genetic brake, and the muscles grow too much, bulging. The boy is healthy, but since myostatin is also made in the heart, he may develop heart problems.

Other species have myostatin mutations. "Double muscling" cattle are valued for their high weights early in life—these animals occur naturally. Chicken breeders lower myostatin production to yield meatier birds, and researchers have created "mighty mice" with blocked myostatin genes to study muscle overgrowth.

Understanding myostatin may have clinical applications. Perhaps blocking myostatin activity to stimulate muscle growth can reverse the ravages of muscular dystrophy and muscle-wasting from AIDS and cancer. But blocking myostatin levels also has the potential for bodybuilding abuse. Performance enhancement isn't the only ethically questionable application of this genetic knowledge. Theoretically, infants could be tested to identify those with myostatin gene variants that predict athletic prowess, given the right training.

As in many matters in human genetics, understanding how this one gene functions has great potential for improving the quality of life for many people—but also presents an opportunity for abuse.



An infant with myostatin deficiency is an overly muscled "superbaby."

Genetics is the study of inherited traits and their variation. Sometimes people confuse genetics with genealogy, which considers relationships but not traits. With the advent of tests that can predict genetic illness, some people have even compared genetics to fortunetelling! But genetics is neither genealogy nor fortunetelling—it is a life science.

## 1.1 Levels of Genetics

**Genes** are the units of heredity. They are biochemical instructions that tell **cells**, the basic units of life, how to manufacture certain proteins. These proteins control the characteristics that create much of our individuality, from our hair and eye color, to the shapes of our body parts, to our talents, personality traits, and health (**figure 1.1**). A gene is composed of the long molecule **deoxyribonucleic acid (DNA)**.



**Figure 1.1 Inherited traits.** This young lady is the proud possessor of an unusual gene variant that confers her red hair, fair skin, and freckles. About 80 percent of individuals like her have a variant of a gene that encodes a protein called the melanocortin 1 receptor—it controls the balance of pigments in the skin.

Some traits are determined almost entirely by genes; most traits, however, also have environmental components. The complete set of genetic instructions characteristic of an organism, including protein-encoding genes and other DNA sequences, constitutes a **genome**. We have known the sequence of the human genome since 2000, but researchers are still determining what all the information does, and how genes interact. This will take many years.

Genetics directly affects our lives, as well as those of our relatives, including our descendants. Principles of genetics also touch history, politics, economics, sociology, art, and psychology. Genetic questions force us to wrestle with concepts of benefit and risk, even tapping our deepest feelings about right and wrong. A field of study called **bioethics** was founded in the 1970s to address personal issues that arise in applying medical technology. Bioethicists today confront concerns that new genetic knowledge raises, such as privacy, confidentiality, and discrimination.

An even newer field than genetics is **genomics**, which considers many genes at a time. Genomics deals with the more common illnesses influenced by many genes that interact with each other and the environment. Considering genomes also enables us to compare ourselves to other species, as in the myostatin mutation seen in humans, cattle, chickens, and mice, discussed in the chapter opening essay. The similarities among genomes of different species can be astonishing and humbling.

Many of the basic principles of genetics were discovered before DNA was recognized as the genetic material, from experiments and observations on patterns of trait transmission in families. For many years, genetics textbooks (such as this one) presented concepts in the order that they were understood, discussing pea plant experiments before DNA structure. Now, since even gradeschoolers know what DNA is, a “sneak preview” of DNA structure and function is appropriate (**Reading 1.1**) to consider the early discoveries in genetics (Chapter 4) from a modern perspective.

Genetics considers the transmission of information at several levels. It begins with the molecular level and broadens through cells, tissues and organs, individuals, families, and finally to populations and the evolution of species (**figure 1.2**).

## DNA

Genes consist of sequences of four types of DNA building blocks, or bases—adenine, guanine, cytosine, and thymine, abbreviated A, G, C, and T. Each base bonds to a sugar and a phosphate group to form a unit called a nucleotide, and nucleotides are linked into long DNA molecules. In genes, DNA bases provide an alphabet of sorts. Each consecutive three DNA bases is a code for a particular amino acid, and amino acids are the building blocks of proteins. Another type of molecule, **ribonucleic acid (RNA)**, uses the information in certain DNA sequences to construct specific proteins. These proteins confer the trait. DNA remains in the part of the cell called the nucleus, and is passed on when a cell divides.

Proteomics is a field that considers the types of proteins made in a particular type of cell. A muscle cell, for example, requires abundant contractile proteins, whereas a skin cell contains mostly scaly proteins called keratins. A cell’s proteomic profile changes as conditions change. A cell lining the stomach, for example, would produce more protein-based digestive enzymes when food is present.

The human genome has about 20,600 protein-encoding genes. Those known to cause disorders or traits are described in a database called Online Mendelian Inheritance in Man. It can be accessed through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). Throughout this text, the first mention of a disease includes its OMIM number.

Despite knowing the sequence of DNA bases of the human genome, there is much we still do not know. For example, very little of the DNA is the human genome actually encodes protein. The rest includes many highly repeated sequences that assist in protein synthesis or turn protein-encoding genes on or off, and other sequences whose roles are yet to be discovered.

## Genes, Chromosomes, and Genomes

The same protein-encoding gene may vary slightly in base sequence from person to person. These variants of a gene are called **alleles**. The changes in DNA sequence that distinguish alleles arise by a process called



## Reading 1.1

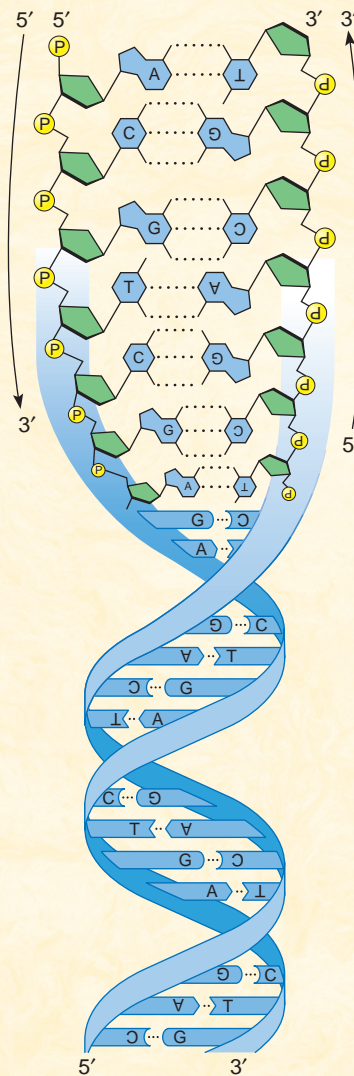
### Introducing DNA

We have probably wondered about heredity since our beginnings, when our distant ancestors noticed family traits such as a beaked nose or unusual talent. Awareness of heredity appears in ancient Jewish law that excuses a boy from circumcision if his brothers or cousins bled to death following the ritual. Nineteenth-century biologists thought that body parts controlled traits, and they gave the hypothetical units of inheritance such colorful names as “pangens,” “ideoblasts,” “gemules,” and simply “characters.”

When Gregor Mendel meticulously bred pea plants in the late nineteenth century to follow trait transmission, establishing the basic laws of inheritance, he inferred that units of inheritance of some kind were at play. His work is all the more amazing because he had no knowledge of cells, chromosomes, or DNA. This short reading recounts, very briefly, what Mendel did not know—that is, the nature of DNA, and how it confers inherited traits.

DNA resembles a spiral staircase or double helix in which the “rails” or backbone is the same from molecule to molecule, but the “steps” are pairs of four types of building blocks, or DNA bases, whose sequence varies (**Figure 1**). The chemical groups that form the steps are adenine (A) and thymine (T), which attract, and cytosine (C) and guanine (G), which attract. The two strands are oriented in opposite directions. A, T, C, and G are called bases, for short. DNA functions as the genetic material because it holds information in the sequences of A, T, C, and G.

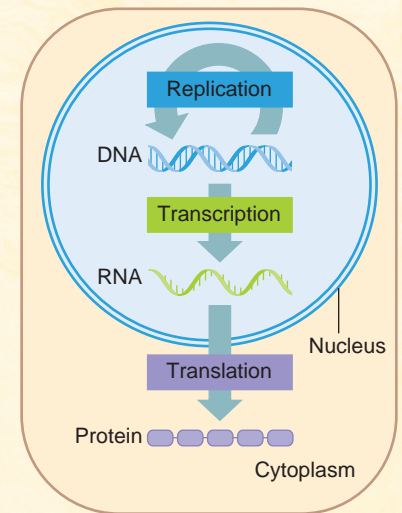
DNA uses its information in two ways. If the sides of the helix part, each half can reassemble its other side by pulling in free building blocks—A and T attracting and G and C attracting. This process, called DNA replication, is essential to maintain the information when the cell divides. DNA also directs the production of specific proteins. In a process called transcription, the sequence of part of one strand of a DNA molecule is copied into a related molecule,



**Figure 1 The DNA double helix.**

(The 5' and 3' labels indicate the head-to-tail organization of the DNA double helix, discussed further in chapter 9.)

messenger RNA. Each three such RNA bases in a row attract another type of RNA that functions as a connector, bringing with it a particular amino acid, which is a building block of protein. The building of a protein is called translation. As the two types of RNA temporarily bond, the amino acids align and join, forming a protein that is then released.



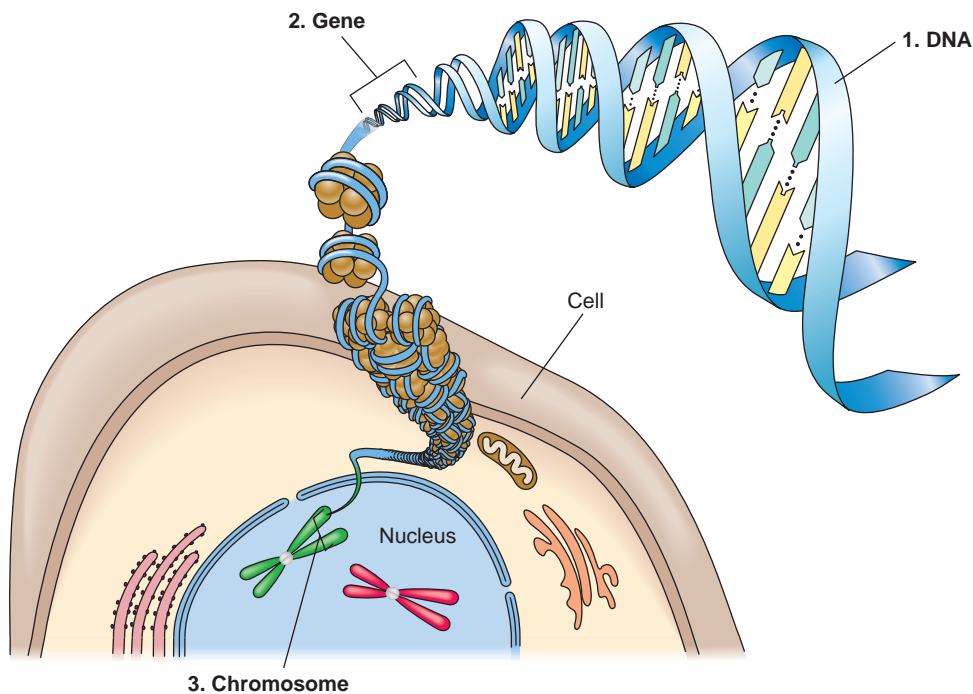
**Figure 2 The language of life:** DNA to RNA to protein.

DNA, RNA, and proteins can be thought of as three related languages (**Figure 2**).

Knowing the nature of a protein can explain how it confers a trait or illness. Consider sickle cell disease, in which red blood cells bend into crescent shapes that lodge in tiny blood vessels, blocking oxygen delivery (OMIM 603903). The altered part of the protein (beta globin) has a single “wrong” DNA base. The replaced amino acid causes the globin molecules to attach to each other differently, forming sticky sheets where oxygen level is low. This action, in turn, distorts the shapes of the red blood cells containing the abnormal proteins. The result of the blocked circulation: strokes, blindness, kidney damage, and severe pain in the hands and feet.

Identifying the exact alteration in a gene and understanding if and how the affected protein disrupts normal functions provides valuable information for developing new treatments. Discovering how a gene functions, however, is only the beginning of explaining how a trait arises, because proteins interact with each other and with signals from the environment in complex ways.





4. Human genome (23 chromosome pairs)



**Figure 1.2 Levels of genetics.** Genetics can be considered at several levels, from DNA, to genes, to chromosomes, to genomes, to the more familiar individuals, families, and populations. (A gene is actually several hundred or thousand DNA bases long.)

**mutation.** Once a gene mutates, the change is passed on when the cell that contains it divides. If the change is in a sperm or egg cell that becomes a fertilized egg, it is passed to the next generation.

Some mutations cause disease, and others provide variation, such as freckled skin. Some mutations may help. For example, a mutation makes a person's cells unable to manufacture a surface protein that binds HIV. These people are resistant to HIV infection. The myostatin mutation in the German family described in the chapter opener is an advantage to an athlete. Many mutations have no visible effect because they do not change the encoded protein in a way that affects its function, just as a minor spelling *error* does not obscure the meaning of a sentence.

Parts of the DNA sequence can vary among individuals, yet not change a person's appearance or health. Such a variant in sequence that is present in at least 1 percent of a population is called a polymorphism, which means "many forms." The genome includes millions of single base sites that differ among individuals. These are called **single nucleotide polymorphisms (SNPs)**, pronounced "snips"). SNPs can cause disease or just mark places in the genome where people differ. A huge research effort

currently focuses on identifying combinations of SNPs that are found almost exclusively among people with a particular disorder. These SNP patterns are then used to estimate disease risks.

DNA molecules are very long. They wrap around proteins and wind tightly, forming structures called **chromosomes**. A human somatic (non-sex) cell has 23 pairs of chromosomes. Twenty-two pairs are **autosomes**, which do not differ between the sexes. The autosomes are numbered from 1 to 22, with 1 the largest. The other two chromosomes, the X and the Y, are **sex chromosomes**. The Y chromosome bears genes that determine maleness. In humans, a female has two X chromosomes and a male has one X and one Y. Charts called **karyotypes** display the chromosome pairs from largest to smallest.

A human cell has two complete sets of genetic information. The 20,600 or more protein-encoding genes are scattered among 3 billion DNA bases in each set of 23 chromosomes.

## Cells, Tissues, and Organs

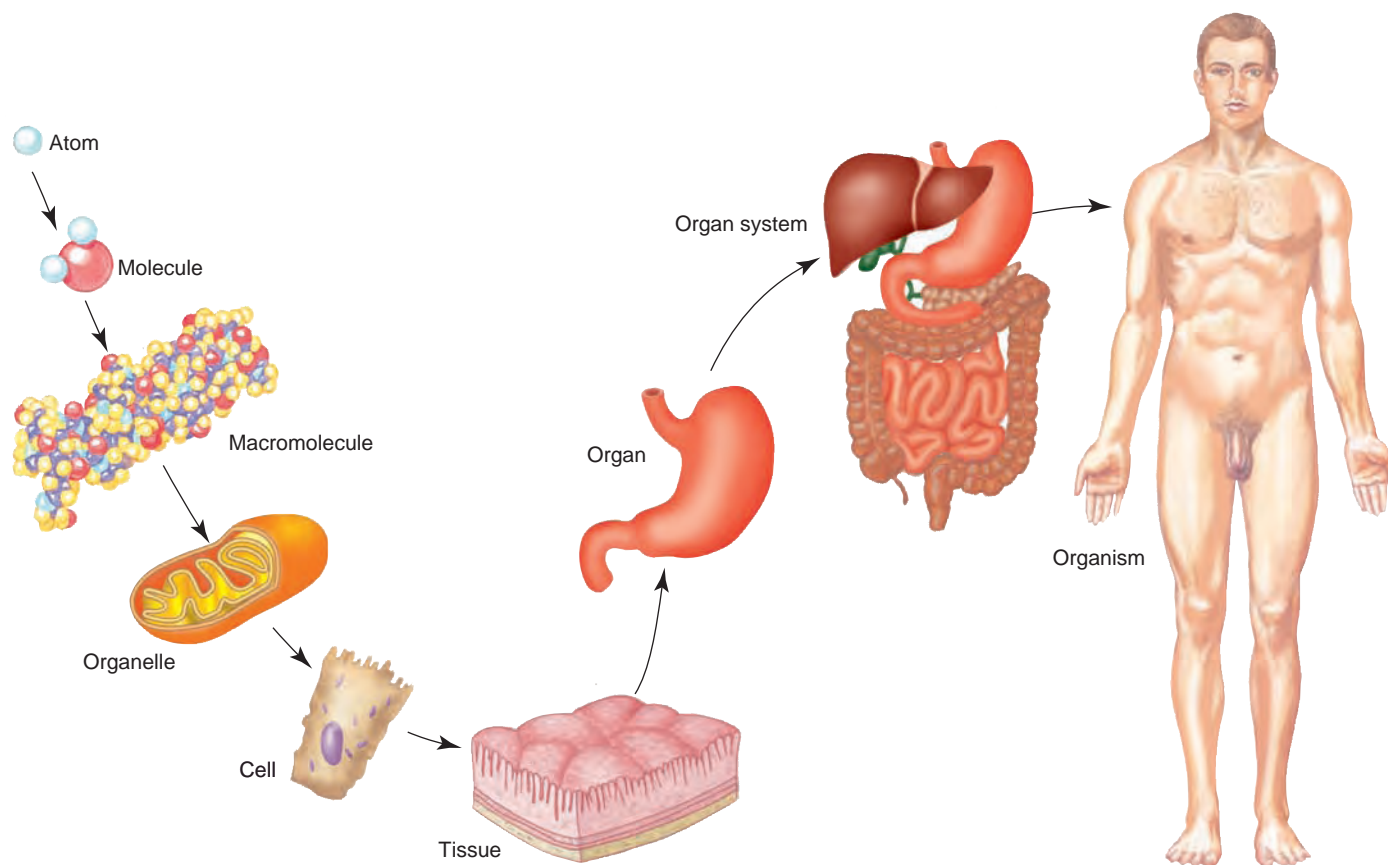
A human body consists of trillions of cells. All cells except red blood cells contain all of the genetic instructions, but cells differ in

appearance and function because they use only some of their genes. The expression of different subsets of genes drives the **differentiation**, or specialization, of distinctive cell types. A muscle cell manufactures its abundant contractile protein fibers, but not the scaly keratins that fill skin cells, or the collagen and elastin proteins of connective tissue cells. All three cell types, however, have complete genomes. Differentiated cells aggregate and interact, forming tissues, which in turn aggregate and interact to form organs and organ systems (**figure 1.3**).

Parts of some organs are made up of rare, unspecialized stem cells that can divide to yield another stem cell and a cell that differentiates. Thanks to stem cells, organs can maintain a reserve supply of cells to grow and repair damage. Yet stem cells are normally tightly controlled—lifting of this control in the German boy described in the chapter-opening case study led to overgrowth of his muscles.

## Individual

Two terms distinguish the alleles that are *present* in an individual from the alleles that are *expressed*. The **genotype** refers to the underlying instructions (alleles present), while the **phenotype** is the visible trait,



**Figure 1.3** Levels of biological organization.

biochemical change, or effect on health (alleles expressed). Alleles are further distinguished by how many copies it takes to affect the phenotype. A **dominant** allele has an effect when present in just one copy (on one chromosome), whereas a **recessive** allele must be present on both chromosomes to be expressed.

## Family

Individuals are genetically connected into families. A person has half of his or her genes in common with each parent and each sibling, and one-quarter with each grandparent. First cousins share one-eighth of their genes.

For many years, transmission (or Mendelian) genetics dealt with single genes in families. Today family genetic studies may consider more than one gene at a time, or traits that have substantial environmental components. That is, the scope of transmission genetics has greatly broadened in recent years. Molecular genetics, which considers DNA, RNA, and proteins, often begins with transmission genetics, when an interesting

family trait or illness comes to a researcher's attention. Charts called **pedigrees** represent the members of a family and indicate which individuals have particular inherited traits. Chapter 4 includes many pedigrees.

## Population

Above the family level of genetic organization is the population. In a strict biological sense, a population is a group of interbreeding individuals. In a genetic sense, a population is a large collection of alleles, distinguished by their frequencies. People from a Swedish population, for example, would have a greater frequency of alleles that specify light hair and skin than people from a population in Ethiopia, who tend to have dark hair and skin. The fact that groups of people look different and may suffer from different health problems reflects the frequencies of their distinctive sets of alleles. All the alleles in a population constitute the gene pool. (An individual does not have a gene pool.)

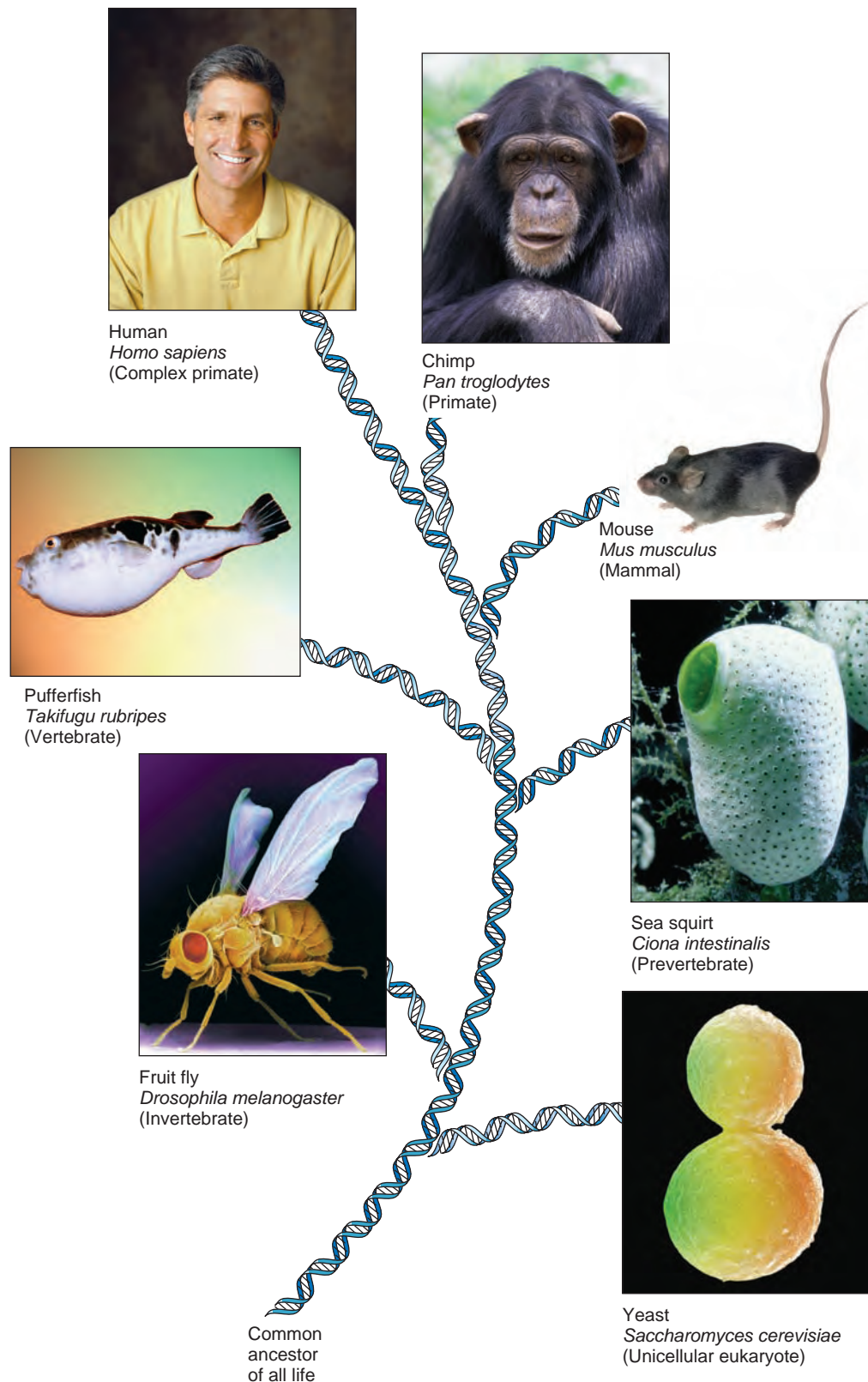
Population genetics is applied in health care, forensics, and other fields. It is also the basis of evolution, which is defined as

changing allele frequencies in populations. These small-scale genetic changes foster the more obvious species distinctions we most often associate with evolution.

## Evolution

Comparing DNA sequences for individual genes, or the amino acid sequences of the proteins that the genes encode, can reveal how closely related different types of organisms are (**figure 1.4**). The underlying assumption is that the more similar the sequences are, the more recently two species diverged from a shared ancestor. This is a more plausible explanation than two species having evolved similar or identical gene sequences by chance.

Genome sequence comparisons reveal more about evolutionary relationships than comparing single genes, simply because there are more data. Humans, for example, share more than 98 percent of the DNA sequence with chimpanzees. Our genomes differ from theirs more in gene organization and in the number of copies of genes than in the overall sequence. Learning the



**Figure 1.4 Genes and genomes reveal our place in the world.** All life is related, and different species share a basic set of genes that makes life possible. The more closely related we are to another species, the more genes we have in common. This illustration depicts how humans are related to certain contemporaries whose genomes have been sequenced.

During evolution, species diverged from shared ancestors. For example, humans diverged more recently from chimps, our closest relative, than from mice, pufferfish, sea squirts, flies, or yeast.



Table 1.1

## A Mini-Glossary of Genetic Terms

Term	Definition
Allele	An alternate form of a gene; a gene variant.
Autosome	A chromosome that does not include a gene that determines sex.
Chromosome	A structure, consisting of DNA and protein, that carries the genes.
DNA	Deoxyribonucleic acid; the molecule whose building block sequence encodes the information that a cell uses to construct a particular protein.
Dominant	An allele that exerts an effect when present in just one copy.
Gene	A sequence of DNA that has a known function, such as encoding protein or controlling gene expression.
Gene pool	All of the genes in a population.
Genome	A complete set of genetic instructions in a cell, including DNA that encodes protein as well as other DNA.
Genotype	The allele combination in an individual.
Karyotype	A size-order display of chromosomes.
Mendelian trait	A trait completely determined by a single gene.
Multifactorial trait	A trait determined by one or more genes and by the environment; also called a complex trait.
Mutation	A change in a gene that affects the individual's health, appearance, or biochemistry.
Pedigree	A diagram used to follow inheritance of a trait in a family.
Phenotype	The observable expression of an allele combination.
Polymorphism	A site in a genome that varies in 1 percent or more of a population.
Recessive	An allele that exerts an effect only when present in two copies.
RNA	Ribonucleic acid; the molecule that enables a cell to synthesize proteins using the information in DNA sequences.
Sex chromosome	A chromosome that carries genes whose presence or absence determines sex.

functions of the human-specific genes may explain the differences between us and them—such as our lack of hair and use of spoken language. Reading 16.1 highlights some of our distinctively human traits.

At the level of genetic instructions for building a body, we are not very different from other organisms. Humans also share many DNA sequences with mice, pufferfish, and fruit flies. Dogs get many of the same genetic diseases that we do! We even share some genes necessary for life with simple organisms such as yeast and bacteria.

Comparisons of people at the genome level reveal that we are much more alike genetically than are other mammals. It's odd to think that chimpanzees are more distinct from each other than we are! Among modern humans, the most genetically diverse are Africans because Africa is where humanity arose. The gene variants among different modern ethnic groups are all subsets of our ancestral African gene pool.

**Table 1.1** presents the basic vocabulary of genetics.

## Key Concepts

1. Genetics is the study of inherited traits and their variation.
2. Genetics can be considered at the levels of DNA, genes, chromosomes, genomes, cells, tissues, organs, individuals, families, and populations.
3. A gene can exist in more than one form, or allele.
4. Comparing genomes among species reveals evolutionary relatedness.

## 1.2 Most Genes Do Not Function Alone

The field of genetics once dealt mostly with traits and illnesses that are clearly determined by single genes. These are called single-gene or Mendelian traits. This may have been an overly simple view. Most genes do not function alone but are influenced by the actions of other genes, as well as by

factors in the environment. For example, a number of genes control how we metabolize nutrients—that is, how much energy (calories) we extract from food. However, the numbers and types of bacteria that live in our intestines vary from person to person, and these microbes affect how many calories we extract from food. This is one reason why some people can eat a great deal and not gain weight, yet others gain weight easily. Studies show that an item of food—such as a 110-calorie cookie—may yield 110 calories in one person's body, but only 90 in another's.

**Multifactorial**, or complex, traits are those that are determined by one or more genes and the environment (**figure 1.5**). (The term *complex traits* has different meanings in a scientific and a popular sense, so this book uses the more precise term *multifactorial*.)

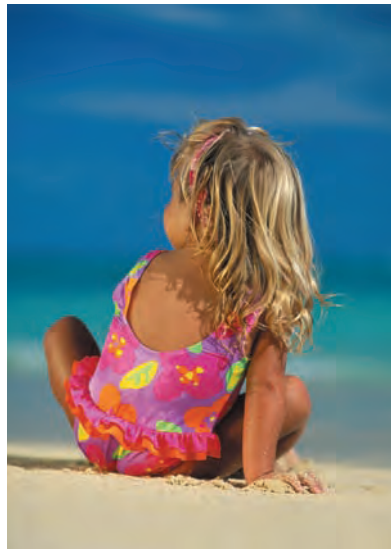
Complicating matters further is the fact that some illnesses occur in different forms—they may be inherited or not, and if inherited, may be caused by one gene or more than one. Usually the inherited forms of an



a.

### Figure 1.5 Mendelian versus multifactorial traits.

(a) Polydactyly—extra fingers and/or toes—is a Mendelian trait (single-gene). (b) Hair color is multifactorial, controlled by at least three genes plus environmental factors such as the bleaching effects of sun exposure.



b.

illness are rarer, as is the case for Alzheimer disease, breast cancer, and Parkinson disease. Researchers can develop treatments based on the easier-to-study inherited form of an illness that can then be used to treat the more common, multifactorial forms. For example, cholesterol-lowering drugs were developed from work on the one-in-a-million children with familial hypercholesterolemia (OMIM 144010) (see figure 5.2).

## Genes and Disease Risk

Knowing whether a trait or illness is single-gene or multifactorial is important for predicting the risk of recurrence. The probability that a single-gene trait will occur in a particular family member is simple to calculate using the laws that Mendel derived, discussed in chapter 4. In contrast, predicting the recurrence of a multifactorial trait is difficult because several contributing factors are at play.

One form of inherited breast cancer illustrates how the fact that genes rarely act alone can complicate the calculation of risk. Mutations in a gene called *BRCA1* cause fewer than 5 percent of all cases of breast cancer (OMIM 113705). In Jewish families of eastern European descent (Ashkenazim), the most common *BRCA1* mutation confers an 86 percent chance of developing the disease over a lifetime. But women from other ethnic groups who inherit this allele have only a 45 percent chance.

The different incidence of disease associated with inheriting the same gene, depending

upon one's population group, reflects the influence of genes other than *BRCA1*. (*Incidence* refers to the frequency of a condition in a population. *Prevalence* refers to how common a condition is in a particular area at a particular time.)

Environmental factors may also affect the *BRCA1* gene's expression. For example, exposure to pesticides that mimic the effects of the hormone estrogen may contribute to causing breast cancer. It can be difficult to tease apart these genetic and environmental influences. *BRCA1* breast cancer, for example, is especially prevalent in Long Island, New York. This population includes both many Ashkenazim and many people exposed to pesticides.

## Genetic Determinism

The fact that the environment modifies gene actions counters the idea of **genetic determinism**, which is that an inherited trait is inevitable. The idea that “we are our genes” can be very dangerous. In predictive testing for inherited disease, which detects a disease-causing allele in a person without symptoms, results are presented as risks, rather than foregone conclusions, because the environment can modify gene expression. A woman might be told “You have a 45 percent chance of developing *BRCA1* breast cancer,” not, “You will get breast cancer.” Conversely, a person can inherit normal *BRCA1* genes, yet develop a different form of breast cancer.

Genetic determinism may be harmful or helpful, depending upon how we apply it.

As part of social policy, genetic determinism can be disastrous. An assumption that one ethnic group is genetically less intelligent than another can lead to lowered expectations and/or fewer educational opportunities for those perceived as biologically inferior. Environment, in fact, has a huge impact on intellectual development.

Identifying the genetic component to a trait can, however, be helpful in that it gives us more control over our health by guiding us in influencing non-inherited factors, such as diet. This is the case for the gene that encodes a liver enzyme called

hepatic lipase. It controls the effects of eating a fatty diet by regulating the balance of LDL (“bad cholesterol”) to HDL (“good cholesterol”) in the blood after such a meal. Inherit one allele and a person can eat a fatty diet yet have a healthy cholesterol profile. Inherit a different allele and a slice of chocolate cake or a fatty burger sends LDL up and HDL down—an unhealthy cholesterol profile.

## Key Concepts

1. Inherited traits are determined by one gene (Mendelian) or by one or more genes and the environment (multifactorial).
2. Even the expression of single genes is affected to some extent by the actions of other genes.
3. Genetic determinism is the idea that an inherited trait cannot be modified.

## 1.3 Applications of Genetics

Barely a day goes by without some mention of genetics in the news. Genetics is impacting many areas of our lives, from health care choices, to what we eat and wear, to unraveling our pasts and controlling our futures. Thinking about genetics evokes fear, hope, anger, and wonder, depending on context and circumstance. Following are glimpses of applications of genetics that we will explore more fully in subsequent chapters.

## Establishing Identity and Ancestry

Comparing DNA sequences to establish or rule out identity, relationships, or ancestry is becoming routine. This approach, called DNA profiling, has many applications.

### Forensics

Before September 11, 2001, the media reported on DNA profiling (also known as DNA fingerprinting) rarely, usually to identify plane crash victims or to provide evidence in high-profile criminal cases. After the 2001 terrorist attacks, investigators compared DNA sequences in bone and teeth collected from the scenes to hair and skin samples from hairbrushes, toothbrushes, and clothing of missing people, and to DNA samples from relatives. It was a massive undertaking that would soon be eclipsed by two natural disasters—to identify victims of the tsunami in Asia in 2004 and hurricane Katrina in the United States in 2005.

A more conventional forensic application matches a rare DNA sequence in tissue left at a crime scene to that of a sample from a suspect. This is statistically strong evidence that the accused person was at the crime scene (or that someone planted evidence). DNA databases of convicted felons often provide “cold hits” when DNA at a crime scene matches a criminal’s DNA in the database. This is especially helpful when there is no suspect.

DNA profiling is used to overturn convictions, too. Illinois has led the way; there, in 1996, DNA tests exonerated the Ford Heights Four, men convicted of a gang rape and double murder who had spent eighteen years in prison, two of them on death row. In 1999, the men received compensation of \$36 million for their wrongful convictions. A journalism class at Northwestern University initiated the investigation that gained the men their freedom. The case led to new state laws granting death row inmates new DNA tests if their convictions could have arisen from mistaken identity, or if DNA tests were performed when they were far less accurate. In 2003, Governor George Ryan was so disturbed by the number of overturned convictions based on DNA evidence that shortly before he left office, he commuted the sentences of everyone on death row to life imprisonment.

DNA profiling helps adopted individuals locate blood relatives. The Kinsearch Registry maintains a database of DNA information on people adopted in the United States from China, Russia, Guatemala, and South Korea, the sources of most foreign adoptions. Adopted individuals can provide a DNA sample and search the database by country of origin to find siblings.

### Rewriting History

DNA analysis can help to flesh out details of history. Consider the offspring of Thomas Jefferson’s slave, Sally Hemings (**figure 1.6**). Rumor at the time placed Jefferson near Hemings nine months before each of her seven children was born, and the children themselves claimed to be presidential offspring. A Y chromosome analysis revealed that Thomas Jefferson could have fathered Hemings’s youngest son, Eston—but so could any of 26 other Jefferson family members. The Y chromosome, because it is only in males, passes from father to son. Researchers identified very unusual DNA sequences on the Y chromosomes of descendants of Thomas Jefferson’s paternal uncle, Field Jefferson. (These men were checked because the president’s only son with wife Martha died in infancy, so he had no direct descendants.) The Jefferson fami-

ly’s unusual Y chromosome matched that of descendants of Eston Hemings, supporting the talk of the time.

Reaching farther back, DNA profiling can clarify relationships from Biblical times. Consider a small group of Jewish people, the cohanim, who share distinctive Y chromosome DNA sequences and enjoy special status as priests. By considering the number of DNA differences between cohanim and other Jewish people, how long it takes DNA to mutate, and the average generation time of 25 years, researchers extrapolated that the cohanim Y chromosome pattern originated 2,100 to 3,250 years ago—which includes the time when Moses lived. According to religious documents, Moses’ brother Aaron was the first priest.

The Jewish priest DNA signature also appears today among the Lemba, a population of South Africans with black skin. Researchers looked at them for the telltale gene variants because their customs suggest a Jewish origin—they do not eat pork (or hippopotamus), they circumcise their newborn sons, and they celebrate a weekly day of rest (**figure 1.7**).

DNA profiling can trace origins for organisms other than humans. For example, researchers analyzed DNA from the leaves of 300 varieties of wine grapes, in search of the two parental strains that gave rise



**Figure 1.6 DNA reveals and clarifies history.** After DNA evidence showed that Thomas Jefferson likely fathered a son of his slave, descendants of both sides of the family met.





**Figure 1.7** Y chromosome DNA sequences reveal origins. The Lemba, a modern people with dark skin, have the same Y chromosome DNA sequences as the cohanim, a group of Jewish priests. The Lemba practiced Judaism long before DNA analysis became available.

to the sixteen major types of wine grapes (**figure 1.8**). One parent, known already, was the bluish-purple Pinot grape. But the second parent, revealed in the DNA, was a surprise—a white grape called Gouais blanc that was so unpopular it hadn’t been cultivated for years and was actually banned during the Middle Ages. Thanks to DNA analysis, vintners now know which parental stocks to preserve.

### Health Care

Looking at disease from a genetic point of view is changing health care. In the past, physicians encountered genetics only as extremely rare disorders caused by single genes. Today, medical science is increasingly recognizing the role that genes play not only in many common conditions, but also in how people react to drugs. Disease is beginning to be seen as the consequence of complex interactions among genes and environmental factors.

In applying genetics to common disorders, it helps to consider how inherited illness caused by a single gene differs from



a.

**Figure 1.8** Surprising wine origins. (a) Gouais blanc and (b) Pinot (noir) grapes gave rise to nineteen modern popular wines, including chardonnay.



b.

other types of illnesses (**table 1.2**). First, we can predict the recurrence risk for single-gene disorders using the laws of inheritance chapter 4 describes. In contrast, an infectious disease requires that a pathogen pass from one person to another—a much less predictable circumstance.

A second key distinction of inherited illness is that the risk of developing symptoms can often be predicted. This is because all genes are present in all cells, even if they are not expressed in every cell. The use of genetic testing to foretell disease is termed predictive medicine. For example, some women who have lost several young relatives to *BRCA1* breast cancer and learn that they have inherited the mutation have their

breasts removed to prevent the cancer. A medical diagnosis, however, is still based on symptoms or observable pathology, such as abnormal cells. This is because some people who inherit mutations associated with particular symptoms never actually develop them. This may happen due to interactions with other genes or environmental factors that are protective in some way, perhaps restoring or substituting for the errant gene’s function.

A third feature of genetic disease is that an inherited disorder may be much more common in some populations than others. Genes do not “like” or “dislike” certain types of people. The reason for such disease clustering is that we tend to pick partners in nonrandom ways, keeping mutations in certain populations. While it might not be “politically correct” to offer a “Jewish genetic disease screen,” as several companies do, it makes biological and economic sense—a dozen disorders are much more common in this population.

So far, tests can identify about 1,000 single-gene disorders, but each year, only about 250,000 people in the United States take these tests. Many people fear that employers or insurers will discriminate based on the results of genetic tests—or even for taking the tests. Yet millions of people regularly have their cholesterol checked!

Table 1.2	
How Single-Gene Diseases Differ from Other Diseases	
1.	Risk can be predicted for family members.
2.	Predictive (presymptomatic) testing may be possible.
3.	Different populations may have different characteristic disease frequencies.
4.	Correction of the underlying genetic abnormality may be possible.

The Bioethics box on page 13 follows two young women as they take genetic tests.

In the United States, legislation to prevent the misuse of genetic information in the insurance industry has been in development since 1993. The 1996 Health Insurance Portability and Accountability Act (HIPAA) stated that genetic information, without symptoms, does not constitute a preexisting condition, and that individuals could not be excluded from group coverage on the basis of a genetic predisposition. The law did not cover individual insurance policies, nor did it stop insurers from asking people to have genetic tests. In 2000, U.S. President Bill Clinton issued an executive order prohibiting the federal government from obtaining genetic information for employees or job applicants and from using such information in promotion decisions. Since then, the Genetic Information Nondiscrimination Act (GINA) has been passed, which is federal legislation that is similar to states' antidiscrimination legislation. Still, many people continue to fear the misuse of genetic information. Some people take genetic tests under false names or do not allow test results to become part of their medical records or are afraid to participate in clinical trials of new treatments.

Genetic tests may actually, eventually, lower health care costs. If people know their inherited risks, they can forestall or ease symptoms that environmental factors might trigger—for example, by eating healthy foods, not smoking, exercising regularly, avoiding risky behaviors, having frequent medical exams, and beginning treatment earlier.

A few genetic diseases can be treated. Supplying a missing protein can prevent some symptoms, such as providing a clotting factor to a person who has a bleeding disorder. Gene therapy replaces instructions for producing the protein in the cells that are affected in the illness.

Many diagnostic tests and treatments for genetic disorders are possible because of initial, “pre-clinical” research using other species that have similar genes to ours. This is the case for lissencephaly (OMIM 607432), which is Greek for “smooth brain.” The brains of affected children lack the characteristic coils of the cortex region, which

causes severe mental retardation, seizures, and shortened life span. To study how this rare disorder unfolds during development, which cannot be done on human embryos and fetuses, researchers used a well-studied roundworm. It has a gene very similar in DNA sequence to the human lissencephaly gene. When mutant, the gene causes worms to have seizures! Although the worm's 302-celled brain is much too simple to coil, it lacks a key “motor molecule” that normally shuttles cell contents to appropriate places. Researchers are now focusing on this molecule to discover how similarly misguided nerve cells affect a human embryo's forming brain.

## Agriculture

The field of genetics arose from agriculture. Traditional agriculture is the controlled breeding of plants and animals to select individuals with certain combinations of inherited traits that are useful to us, such as seedless fruits or lean meat. **Biotechnology**, the use of organisms to produce goods (including foods and drugs) or services, is an outgrowth of agriculture. One ancient example of biotechnology is using microorganisms to ferment fruits to manufacture alcoholic beverages, a technique the Babylonians used by 6000 B.C.

Traditional agriculture is imprecise because it shuffles many genes—and, therefore, many traits—at a time. In contrast, the application of DNA-based techniques, part of modern biotechnology, enables researchers to manipulate one gene at a time. This adds control and precision that is not part of traditional agriculture. Organisms altered to have new genes or to over- or underexpress their own genes are termed “genetically modified” (GM). If the organism has genes from another species, it is termed transgenic. Golden rice, for example, manufactures twenty-three times as much beta carotene (a vitamin A precursor) as unaltered rice. It has “transgenes” from corn and bacteria. Golden rice also stores twice as much iron as unaltered rice because one of its own genes is overexpressed. These nutritional boosts bred into edible rice strains may help prevent vitamin A and iron deficiencies in people who eat them.

People in the United States have been safely eating GM foods for more than a

decade. In Europe, many people object to GM foods, on ethical grounds or based on fear. Officials in France and Austria have called such crops “not natural,” “corrupt,” and “heretical.” **Figure 1.9** shows an artist's rendition of these fears. Food labels in Europe, and some in the United States, indicate whether a product is “GM-free.” Some objections to GM foods arise from lack of knowledge. A public opinion poll in the United Kingdom discovered, for example, that a major reason citizens avoid GM foods is that they do not want to eat DNA! One British geneticist wryly observed that the average meal provides 150,000 kilometers (about 93,000 miles) of DNA.

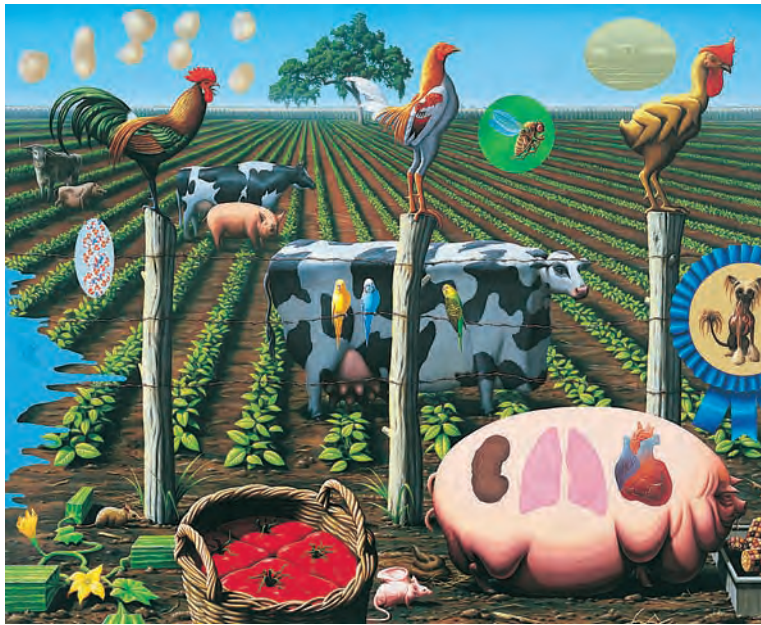
Other concerns about GM organisms may be better founded. Labeling foods can prevent allergic reaction to an ingredient in a food that wouldn't naturally be there, such as a peanut protein in corn. Another objection is that field tests may not adequately predict the effects of GM crops on ecosystems. GM plants have been found far beyond where they were planted, thanks to wind pollination. GM crops may also lead to extreme genetic uniformity, which could be disastrous. Some GM organisms, such as fish that grow to twice normal size or can survive at temperature extremes, may be so unusual that they disrupt ecosystems.

## Ecology

We humans share the planet with many thousands of other species. We aren't familiar with many of our neighbors on the planet because we can't observe their habitats, or we can't grow them in our laboratories. “Metagenomics” is a new field that is revealing and describing much of the invisible living world by sequencing all of the DNA in a particular habitat. Such areas range from soil, to an insect's gut, to garbage. This information is revealing how species interact, and it may even yield new drugs and reveal novel energy sources.

Metagenomics researchers collect and sequence DNA and consult databases of known genes and genomes to imagine what the organisms might be like. One of the first metagenomics projects discovered and described life in the Sargasso Sea. This





**Figure 1.9 An artist's view of biotechnology.** Artist Alexis Rockman vividly captures some fears of biotechnology, including a pig used to incubate spare parts for sick humans, a muscle-boosted, boxy cow, a featherless chicken with extra wings, a mini-warhog, and a mouse with a human ear growing out of its back.

2-million-square-mile oval area off the coast of Bermuda has long been thought to lack life beneath its thick cover of seaweed, which is so abundant that Christopher Columbus thought he'd reached land when his ships came upon it. Many a vessel has been lost in the Sargasso Sea, which includes the area known as the Bermuda Triangle. When researchers sampled the depths, they collected more than a billion DNA bases, representing about 1,800 microbial species, including at least 148 not seen before. More than a million new genes were discovered. Another metagenomics project is collecting DNA from air samples taken in lower Manhattan.

A favorite site for metagenomics analysis is the human body. The mouth, for example, is home to some 500 species of bacteria, only about 150 of which can grow in the laboratory. In addition to describing the ecosystem of the human mouth, metagenomics yields medically useful information. This was the case for *Treponema denticola*, which holds a place in medical history as the first microorganism that the father of microscopy, Antonie van Leeuwenhoek, sketched in the 1670s. Its genome revealed how it survives amid the films formed by other bacteria in the mouth, and how it causes gum disease. Researchers were surprised to find that this

microorganism is genetically very different from other spiral-shaped bacteria thought to be close relatives—those that cause syphilis and Lyme disease. Therefore, genomics showed that appearance (a spiral shape) does not necessarily reflect the closeness of the evolutionary relationship between two types of organisms.

Metagenomic analysis of the human digestive tract is also interesting at its other end. Analysis of the DNA in stool reveals hundreds of bacterial species. Based on such studies of various body parts, researchers conclude that 90 percent of the cells in the human body (counting the digestive tract) are not actually human! This is possible because microbial cells are so much smaller than ours.

## A Global Perspective

Because genetics so intimately affects us, it cannot be considered solely as a branch of life science. Equal access to testing, misuse of information, and abuse of genetics to intentionally cause harm are compelling issues that parallel scientific progress.

Genetics and genomics are spawning technologies that may vastly improve quality of life. But at first, tests and treatments will be costly and not widely available. While

advantaged people in economically and politically stable nations may look forward to genome-based individualized health care, poor people in other nations just try to survive, often lacking basic vaccines and medicines. In an African nation where two out of five children suffer from AIDS and many die from other infectious diseases, newborn screening for rare single-gene defects hardly seems practical. However, genetic disorders weaken people so that they become more susceptible to infectious diseases, which they can pass to others.

Human genome information can ultimately benefit everyone. Consider drug development. Today, there are fewer than 500 types of drugs. Genome information from humans and our pathogens and parasites is revealing new drug targets. For example, malaria is an infectious disease caused by a single-celled parasite transmitted through the bite of a female mosquito. The genomes of the parasite, mosquito, and human have been sequenced, and within this vast amount of information likely lie clues that researchers can use to develop new types of anti-malarial drugs. Global organizations, including the United Nations, World Health Organization, and the World Bank, are discussing how nations can share new diagnostic tests and therapeutics that arise from genome information. The human genome belongs to us all.

## Key Concepts

1. Genetics has applications in diverse areas. Matching DNA sequences can clarify relationships, which is useful in forensics, establishing identity, and understanding historical events.
2. Inherited disease differs from other disorders in its predictability; predictive testing; characteristic frequencies in different populations; and the potential of gene therapy.
3. Agriculture, both traditional and biotechnological, applies genetic principles.
4. Collecting DNA from habitats and identifying the sequences in databases is a new way to analyze ecosystems.
5. Human genome information has tremendous potential but must be carefully managed.



## Genetic Testing

Taking a genetic test may be as simple as ordering a kit on the Web, swishing a cotton swab on the inside of the mouth, and popping it in the mail. A few days later, results are reported—but often without any guidance as to what they mean (and sometimes accompanied by advice to purchase pricey supplements!). Rather than using such “direct-to-consumer” genetic testing, it is safer to take a genetic test from a health care professional. Such tests detect health-related gene variants most likely to be present in a particular individual, based on clues such as personal health, family history, and ethnic background. This is what two 19-year-old college roommates, Mackenzie and Laurel, decide to do.

Mackenzie requests three panels of tests, based on her family background. An older brother and her father smoke cigarettes and drink too much alcohol, and her father’s mother, also a smoker, died of lung cancer. Two relatives on her mother’s side had colon cancer. Older relatives on both sides have Alzheimer disease. Mackenzie has tests to detect genes that predispose her to developing addictions, certain cancers, and inherited forms of Alzheimer disease.

Laurel requests different tests. She, her sister, and her mother frequently have bronchitis and pneumonia, so she has a test for cystic fibrosis (CF) (OMIM 219700), which can increase susceptibility to respiratory infections.

She also has tests for type 2 diabetes mellitus because relatives have it, and diet and exercise can help control symptoms. Laurel refuses a test for inherited susceptibility to Alzheimer disease, even though a grandfather died of it. She does not want to know if this condition is likely to lie in her future, because it can’t be treated. Finally, she seeks information about her risk of developing heart and blood vessel (cardiovascular) disease because she’s had elevated cholesterol in the past.

Each student proceeds through several steps. The first is to record a complete family history. Next, each student rubs a cotton swab on the inside of her cheek to obtain cells, which are sent to a laboratory for analysis. There, DNA is cut up and displayed on a tiny device called a **microarray** that reveals the gene variants that are present or active.

Microarrays test many genes and are customized to individuals. Mackenzie’s microarrays detect genes that affect addictive behaviors, elevate the risk for developing lung and colon cancer, and are associated with Alzheimer disease. Laurel’s microarrays suit her background and requests, including variants of the CF gene associated with milder symptoms, gene variants that affect how her bloodstream transports glucose, and such traits as blood pressure, blood clotting, and how cells use cholesterol and other lipids.

After the test results are in, a genetic counselor explains the findings. Mackenzie is predisposed to develop addictive behaviors and lung cancer—a dangerous combination—but she does not face increased risk for inherited forms of colon cancer or Alzheimer disease. Laurel has mild CF, which explains her frequent respiratory infections. The microarray indicates which types of infections she is most susceptible to, and which antibiotics will most effectively treat them. The test panel that assessed her cells’ ability to handle glucose reveals her risk of developing diabetes is lower than that for the general population, but she does have several gene variants that raise her blood cholesterol level. The results also indicate which cholesterol-lowering drug will work best, should diet and exercise habits not be enough to counter her inherited tendency to accumulate lipids in the bloodstream.

Mackenzie and Laurel can take additional genetic tests as their interests and health

status change. For example, they might take further tests when they and their partners are considering having a child, or if they become ill with cancer. Genetic tests can detect whether they are carriers for any of several hundred illnesses, because two carriers of the same condition can pass it to offspring even when they are not themselves affected. If either Laurel or Mackenzie is in this situation, then tests on DNA from an embryo or a fetus can determine whether it has inherited the condition.

Illness may prompt Laurel or Mackenzie to seek further testing. If either young woman suspects she may have cancer, for example, a type of microarray called an expression panel can determine which genes are turned on or off in the affected cells sampled from the tumor or from blood. “Gene expression” refers to the cell’s use of the information in the DNA sequence to synthesize a particular protein. In contrast, DNA from cheek lining cells reveals specific gene variants and DNA sequences that are present in all cells of the body.

DNA expression microarrays are very useful in diagnosing and treating cancer. They can identify cancer cells very early, when treatment is more likely to work, estimate if and how quickly the disease will progress, and even indicate which drugs are likely to be effective and which will likely produce intolerable side effects.

Laurel and Mackenzie’s genetic test results will be kept confidential, even though they may reveal risks that apply to other family members. Laws prevent employers and insurers from discriminating based on genetic information. In general, insurance companies decide whom to insure and at what rates based on symptoms present before or at the time of request for coverage. The results of genetic tests are not clinical diagnoses or even predictions, but probability statements about how likely certain symptoms are to arise in an individual.



# Summary

## 1.1 Levels of Genetics

1. **Genes** are the instructions to manufacture proteins, which determine inherited traits.
2. A **genome** is a complete set of genetic information. A **cell** contains two genomes of **DNA**. **Genomics** is the study of many genes and their interactions.
3. Genes encode proteins and the **RNA** molecules that carry out protein synthesis. RNA carries the gene sequence information so that it can be utilized, while the DNA is transmitted when the cell divides. Much of the genome does not encode protein.
4. Variants of a gene, called **alleles**, arise by **mutation**. They may differ slightly from one another, but encode the same product. A polymorphism is a site or sequence of DNA that varies in one percent or more of a population. The **phenotype** is the gene's expression. An allele combination constitutes the **genotype**. Alleles may be **dominant** (exerting an effect in a single copy) or **recessive** (requiring two copies for expression).
5. **Chromosomes** consist of DNA and protein. The 22 types of **autosomes** do not include genes that specify sex. The X and Y **sex chromosomes** bear genes that determine sex.
6. The human genome consists of about 3 billion DNA bases. Cells **differentiate** by expressing subsets of genes. **Stem cells** divide to yield other stem cells and cells that differentiate.
7. Pedigrees are diagrams used to study traits in families.
8. Genetic populations are defined by their collections of alleles, termed the gene pool.
9. Genome comparisons among species reveal evolutionary relationships.

## 1.2 Most Genes Do Not Function Alone

10. Single genes determine Mendelian traits.
11. **Multifactorial** traits reflect the influence of one or more genes and the environment. Recurrence of a Mendelian trait is predicted based on Mendel's laws; predicting the recurrence of a multifactorial trait is more difficult.

12. Genetic determinism is the idea that the expression of an inherited trait cannot be changed.

## 1.3 Applications of Genetics

13. DNA profiling can establish identity, relationships, and origins.
14. In inherited diseases, recurrence risks are predictable and a mutation may be detected before symptoms arise. Some inherited disorders are more common among certain population groups. Gene therapy attempts to correct mutations. Studying genes and genomes of nonhuman animals can help us understand causes of diseases in humans.
15. Genetic information can be misused.
16. Agriculture is selective breeding. **Biotechnology** is the use of organisms or their parts for human purposes. A transgenic organism harbors a gene or genes from a different species.
17. In metagenomics, DNA collected from habitats is used to reconstruct ecosystems.

# Review Questions

1. Place the following terms in size order, from largest to smallest, based on the structures or concepts they represent:
  - a. chromosome
  - b. gene pool
  - c. gene
  - d. DNA
  - e. genome
2. Distinguish between:
  - a. an autosome and a sex chromosome
  - b. genotype and phenotype
  - c. DNA and RNA
  - d. recessive and dominant traits
  - e. pedigrees and karyotypes
  - f. gene and genome
3. List four ways that inherited disease differs from other types of illnesses.
4. Cystic fibrosis is a Mendelian trait; height is a multifactorial trait. How do the causes of these characteristics differ?
5. Mutants are often depicted in the media as being abnormal, ugly, or evil. Why is this not necessarily true?
6. Health insurance forms typically ask for applicants to list existing or preexisting symptoms. How do the results of a genetic test differ from this?
7. List an advantage and a disadvantage of growing genetically modified crops.

# Applied Questions

1. Genome sequences may contain information that can be useful, such as in providing new diagnostic tests and treatments. However, genome sequences may also contain information that could be used for negative applications, such as developing biological weapons. Should researchers publish genome sequences of pathogens, or should such information be restricted to prevent the development of bioweapons? Cite a reason for your answer.
2. Two roommates go grocery shopping and purchase several packages of cookies that supposedly each provide 100 calories. After a semester of eating the snacks, one roommate has gained 6 pounds, but the other hasn't. Assuming that other dietary and exercise habits are similar, explain the roommates' different response to the cookies.

3. In a search for a bone marrow transplant donor, why would a patient's siblings be considered before first cousins?
  4. DNA databases of convicted felons have solved many crimes and exonerated many innocent people. What might be the benefits and dangers of establishing databases on everyone? How should such a program be instituted?
  5. Wastewater consists of water that we use in our daily lives. It includes whatever we put down drains and in toilets, runoff from watering lawns and gardens, as well as industrial waste. This material dries into a sludge. How could metagenomics be used to analyze sludge?
- Web Activities**
- Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 1** and **Web Activities** to find the website links needed to complete the following activities.
6. Many artists have been inspired by aspects of genetics, from the symmetry of DNA to common fears of genetic technologies. Visit the websites provided on the OLC, select a work of art, and describe what it represents.
  7. Consult the website for the Council for Responsible Genetics. Select a controversy covered and present both sides of the issue. This may require some additional research!
  8. Consult the Combined DNA Index System (CODIS) of the Federal Bureau of Investigation on the Web. This database utilizes forensic DNA information and computer technology so that the local, state, and federal governments can easily exchange information about suspected criminals. Do you think this information is useful, or an invasion of privacy?
  9. Genetics inspires cartoonists, too. Visit the website provided on the OLC and search under "DNA." Select a cartoon that misrepresents genetics, and explain how it is inaccurate, misleading, or sensationalized.
  10. The Larsons have a child who has inherited cystic fibrosis. Their physician tells them that if they have other children, each faces a 1 in 4 chance of also inheriting the illness. The Larsons tell their friends, the Espositos, of their visit with the doctor. Mr. and Mrs. Esposito are expecting a child, so they ask their physician to predict whether he or she will one day develop multiple sclerosis—Mr. Esposito is just beginning to show symptoms. They are surprised to learn that, unlike the situation for cystic fibrosis, recurrence risk for multiple sclerosis cannot be easily predicted. Why not?
  11. Burlington Northern Santa Fe Railroad asked its workers for a blood sample, and then supposedly tested for a gene variant that predisposes a person for carpal tunnel syndrome, a disorder of the wrists caused by repetitive motion. The company threatened to fire a worker who refused to be tested; the worker sued the company. The Equal Employment Opportunity Commission ruled in the worker's favor, agreeing that the company's action violated the Americans with Disabilities Act.
    - a. Do you agree with the company or the worker? What additional information would be helpful in taking sides?
    - b. How is the company's genetic testing not based on sound science?
    - c. How can tests such as those described for the two students in the Bioethics reading be instituted in a way that does not violate a person's right to privacy, as the worker in the railroad case contended?

Learn to apply the skills of a genetic counselor with this additional case found in the *Case Workbook in Human Genetics*.

Genetics in the news

## A Second Look

1. At the same time the media reported the story of the giant-musclcd German boy, another young man, an 8-year-old poet, died of a muscle-wasting condition. How might a mutation in the myostatin gene cause an effect opposite the one seen in the German boy?
2. If myostatin were to be sold in stores as a nutritional supplement, would you take it to enhance your muscles? What information would you want to have before you take it?
3. Explain how the effects of the myostatin mutation in the German boy can be advantageous but also dangerous.



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.





# Cells

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- 2.3 **Cell-Cell Interactions**
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## STEM CELLS RESTORE SIGHT, BUT NOT VISION

In 1960, three-year-old Michael M. lost his left eye in an accident. Because much of the vision in his right eye was already impaired from scars on the cornea (the transparent outer layer) he could see only distant, dim light. Several corneal transplants failed, adding more scar tissue. At age 39, Michael received stem cells from a donated cornea and the tissue finally regrew. Michael could see his wife and two sons for the first time. But he quickly learned that vision is more than seeing—his brain had to interpret images. Because the development of his visual system had stalled, and he had only one eye, he could discern shapes and colors, but not three-dimensional objects, such as facial details. In fact, he had been more comfortable skiing blind, using verbal cues, than he was with sight—the looming trees were terrifying. It took years for Michael’s brain to catch up to his rejuvenated eye.

Michael’s doctors used stem cells to repair an injury. Stem cells may also correct inherited disorders, such as retinitis pigmentosa (RP) (OMIM 600105). In RP, nerve cells or blood vessels of the retina degenerate, causing blindness. (The retina is a layered structure at the back of the eyeball that sends visual information to the brain.) Stem cells from human bone marrow were injected into one eye of mice with RP. In each animal, the treated eye developed normally, but the retina of the untreated eye degenerated. The injected stem cells divided to yield some cells that specialized to form the linings of blood vessels, and some stem cells, restoring the circulation that rescued the nerve cells in the retina.

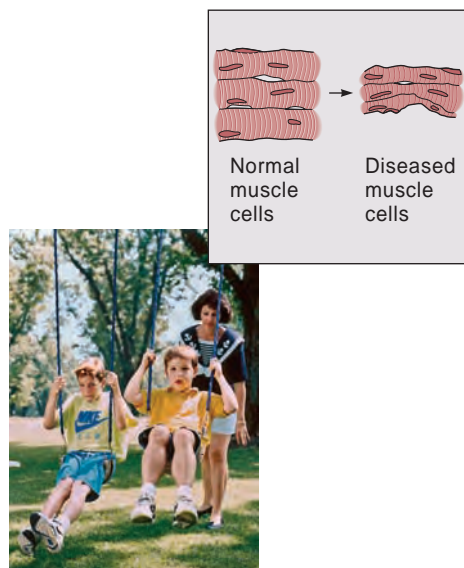
Stem cells are the body’s way of growing and healing. Medical science is trying to harness them to treat a variety of types of disease.



When Michael M. received stem cells to heal his eyes, his sight (sensation of light) was restored, but not his vision (his brain’s perception of the images). Slowly, his brain caught up with his senses, and he was able to see his family for the first time.

The activities and abnormalities of cells underlie our inherited traits, quirks, and illnesses. Understanding cell function reveals how a healthy body works, and how it develops from one cell to trillions. Understanding what goes wrong in certain cells when a disease occurs can suggest ways to treat the condition—we learn what must be repaired or replaced. In Duchenne muscular dystrophy (OMIM 310200), for example, the reason that a little boy's calf muscles are overdeveloped is that he cannot stand normally because other muscles are weak. The affected cells lack a protein that supports the cells' shape during forceful contractions (**figure 2.1**). Identifying the protein revealed exactly what needs to be replaced—but doing so has been difficult.

Our bodies include many variations on the cellular theme. Differentiated cell types include bone and blood, nerve and muscle, and even subtypes of those. Equally important are **stem cells** that replicate themselves and generate differentiated cells when they divide, enabling a body to develop, grow, and repair damage.



**Figure 2.1 Genetic disease at the whole-person and cellular levels.** This young man has Duchenne muscular dystrophy. An early sign of the illness is overdeveloped calf muscles that result from his inability to rise from a sitting position the usual way. Lack of the protein dystrophin causes his skeletal muscle cells to collapse when they contract.

Cells interact. They send, receive, and respond to information. Some cells aggregate with others of like function, forming tissues, which in turn interact to form organs and organ systems. Other cells move about the body. Cell numbers are important, too—they are critical to development, growth, and healing. Staying healthy reflects a precise balance between cell division, which adds cells, and cell death, which takes them away.

## 2.1 The Components of Cells

All cells share certain features that enable them to perform the basic life functions of reproduction, growth, response to stimuli, and energy use. Body cells also have specialized features, such as the contractile proteins in a muscle cell. The more than 260 differentiated cell types in a human body arise because the cells express different subsets of the 24,000 or so protein-encoding genes.

Our cells fall into four broad categories, or tissue types: epithelium (lining cells), muscle, nerve, and connective tissues (including blood, bone, cartilage, and adipose cells). Other multicellular organisms, including other animals, fungi, and plants, also have differentiated cells. Some single-celled organisms, such as the familiar paramecium and ameba, have very distinctive cells as complex as our own. The most abundant organisms on the planet, however, are simpler and single-celled. These microorganisms are nonetheless successful life forms because they have occupied earth much longer than we have.

Biologists recognize three broad varieties of cells that define three major “domains” of life: the Archaea, the Bacteria, and the Eukarya. A domain is a broader classification than the familiar kingdom.

The archaea and bacteria are both single-celled, but they differ from each other in the sequences of many of their genetic molecules and in the types of molecules in their membranes. Archaea and bacteria are, however, both **prokaryotes**, which means that they lack a **nucleus**, the structure that contains DNA in the cells of other types of organisms.

The third domain of life, the Eukarya or **eukaryotes**, includes single-celled organisms

that have nuclei, as well as all multicellular organisms such as ourselves. Eukaryotic cells are also distinguished from prokaryotic cells by structures called **organelles**, which perform specific functions. The cells of all three domains contain globular assemblies of RNA and protein called **ribosomes** that are essential for protein synthesis. The eukaryotes may have arisen from an ancient fusion of a bacterium with an archaean.

## Chemical Constituents of Cells

Cells are composed of molecules. Some of the chemicals of life (biochemicals) are so large that they are called macromolecules.

The major macromolecules that make up cells and are used by them as fuel are **carbohydrates** (sugars and starches), **lipids** (fats and oils), **proteins**, and **nucleic acids**. Cells require vitamins and minerals in much smaller amounts.

Carbohydrates provide energy and contribute to cell structure. Lipids form the basis of several types of hormones, form membranes, provide insulation, and store energy. Proteins have many diverse functions in the human body. They participate in blood clotting, nerve transmission, and muscle contraction and form the bulk of the body's connective tissue. **Enzymes** are especially important proteins because they facilitate, or catalyze, biochemical reactions so that they occur swiftly enough to sustain life. Most important to the study of genetics are the nucleic acids DNA and RNA, which translate information from past generations into specific collections of proteins that give a cell its individual characteristics.

Macromolecules often combine, forming larger structures within cells. For example, the membranes that surround cells and compartmentalize their interiors consist of double layers (bilayers) of lipids embedded with carbohydrates, proteins, and other lipids.

Life is based on the chemical principles that govern all matter; genetics is based on a highly organized subset of the chemical reactions of life. **Reading 2.1** describes some drastic effects that result from major biochemical abnormalities.



## Reading 2.1

# Inborn Errors of Metabolism Affect the Major Biomolecules

Enzymes are proteins that catalyze (speed or facilitate) specific chemical reactions, and therefore control a cell's production of all types of macromolecules. When the gene that encodes an enzyme mutates so that the enzyme is not produced or cannot function, the result can be too much or too little of the product of the biochemical reaction that the enzyme catalyzes. These biochemical buildups and breakdowns may cause symptoms. Genetic disorders that result from deficient or absent enzymes are called "inborn errors of metabolism." Following are some examples.

### Carbohydrates

The newborn yelled and pulled up her chubby legs in pain a few hours after each feeding. She developed watery diarrhea, even though she was breastfed. Finally, a doctor diagnosed *lactase deficiency* (OMIM 223000)—lack of the enzyme lactase, which enables the digestive system to break down the carbohydrate lactose. Bacteria multiplied in the undigested lactose in the child's intestines, producing gas, cramps, and bloating. Switching to a soybean-based, lactose-free infant formula helped. A different disorder with milder symptoms is lactose intolerance (OMIM 150200), common in adults (see the opening essay to chapter 15).

### Lipids

A sudden sharp pain began in the man's arm and spread to his chest—the first sign of a heart attack. At age 36, he was younger than most people who suffer heart attacks, but he had inherited a gene variant that halved the number of protein receptors for cholesterol on his liver cells. Because cholesterol could not enter the liver cells efficiently, it built up in his arteries, constricting blood flow in his heart and eventually causing a mild heart attack. A fatty diet had accelerated his *familial hypercholesterolemia*, but a cholesterol-lowering drug helped.

### Proteins

The first sign that the infant was ill was urine that smelled like maple syrup. Tim

slept most of the time, and he vomited so often that he hardly grew. A blood test revealed *maple syrup urine disease* (OMIM 248600). He could not digest three types of amino acids (protein building blocks), which accumulated in his bloodstream. A diet very low in these amino acids helped.

### Nucleic Acids

From birth, Troy's wet diapers contained orange, sandlike particles, but otherwise he seemed healthy. By six months of age, he was in pain when urinating. A physician noted that Troy's writhing movements were involuntary rather than normal crawling.

The orange particles in Troy's diaper indicated *Lesch-Nyhan syndrome* (OMIM 300322), caused by the deficiency of an enzyme called HGPRT. Troy's body could not recycle two of the four types of DNA building blocks, instead converting them into uric acid, which crystallizes in urine. Other symptoms that began later were not as easy to explain—severe mental retardation, seizures, and aggressive and self-destructive behavior. By age three, he responded to stress by uncontrollably biting his fingers, lips, and shoulders. On doctors' advice, his parents had his teeth removed to keep him from harming himself, and he was kept in restraints. Troy would probably die before the age of 30 of kidney failure or infection.

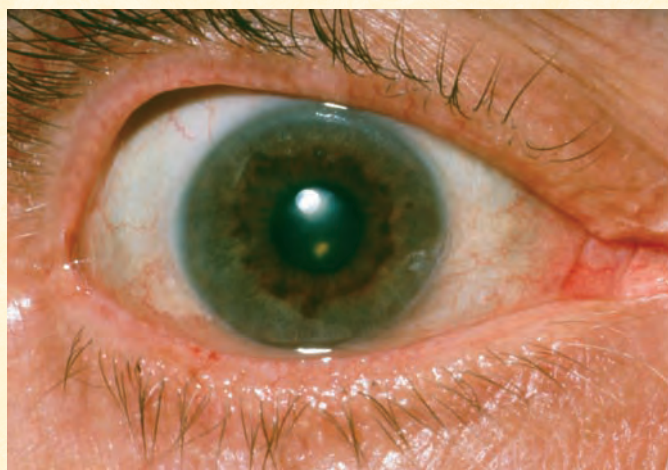
### Vitamins

Vitamins enable the body to use the carbohydrates, lipids, and proteins we eat. Julie inherited *biotinidase deficiency* (OMIM 253260), which greatly slows her body's use of the vitamin biotin. If Julie hadn't been diagnosed as a newborn and quickly started on biotin supplements, by

early childhood she would have shown biotin deficiency symptoms: mental retardation, seizures, skin rash, and loss of hearing, vision, and hair. Her slow growth, caused by her body's inability to extract energy from nutrients, would have eventually proved lethal.

### Minerals

Ingrid, in her thirties, lives in the geriatric ward of a mental hospital, unable to talk or walk. She grins and drools, but she is alert and communicates using a computer. When she was a healthy high-school senior, symptoms of *Wilson disease* (OMIM 277900) began as her weakened liver could no longer control the excess copper her digestive tract absorbed from food. The initial symptoms were stomachaches, headaches, and an inflamed liver (hepatitis). Then other changes began—slurred speech; loss of balance; a gravelly, low-pitched voice; and altered handwriting. A psychiatrist noted the telltale greenish rings around her irises, caused by copper buildup, and diagnosed Wilson disease (**Figure 1**). Finally Ingrid received penicillamine, which enabled her to excrete the excess copper in her urine. The treatment halted the course of the illness, saving her life.



**Figure 1 Wilson disease.** A greenish ring around the brownish iris is one sign of the copper buildup of Wilson disease.



## Organelles

A typical eukaryotic cell holds a thousand times the volume of a bacterial or archaeal cell (**figure 2.2**). To carry out the activities of life in such a large cell, organelles divide the labor by partitioning off certain areas or serving specific functions. The coordinated functioning of the organelles in a eukaryotic cell is much like the organization of departments in a department store. In general, organelles keep related biochemicals and structures close enough to one another to interact efficiently. This eliminates the need to maintain a high concentration of a particular biochemical throughout the cell.

Organelles have a variety of functions. They enable a cell to retain as well as to use its genetic instructions, acquire energy, secrete substances, and dismantle debris. Saclike organelles sequester biochemicals that might harm other cellular constituents. Some organelles consist of membranes studded with enzymes embedded in the order in which they participate in the chemical reactions that produce a particular molecule. **Figure 2.3** depicts organelles.

The most prominent organelle of most cells is the nucleus. It is enclosed in a layer

called the nuclear envelope. Nuclear pores are rings of proteins that allow certain biochemicals to exit or enter the nucleus (**figure 2.4**). Within the nucleus, an area that appears darkened under a microscope, called the nucleolus (“little nucleus”), is the site of ribosome production. The nucleus is filled with DNA complexed with many proteins to form chromosomes. Other proteins form fibers that give the nucleus a roughly spherical shape. RNA is abundant too, as are enzymes and proteins required to synthesize RNA from DNA. The fluid in the nucleus, minus these contents, is called nucleoplasm.

The remainder of the cell—that is, everything but the nucleus, organelles, and the outer boundary, or **plasma membrane**—is the **cytoplasm**. Other cellular components include stored proteins, carbohydrates, and lipids; pigment molecules; and various other small chemicals.

### Secretion—The Eukaryotic Production Line

Organelles interact in ways that coordinate basic life functions and sculpt the characteristics of specialized cell types. Secretion, which is the release of a substance from

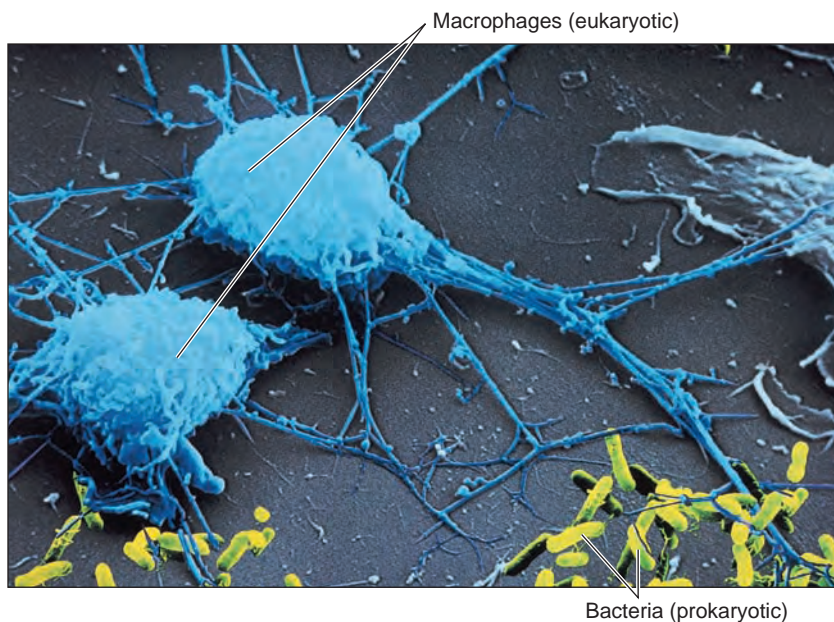
a cell, illustrates how organelles function together.

Secretion begins when the body sends a biochemical message to a cell to begin producing a particular substance. For example, when a newborn first suckles the mother’s breast, the stimulation causes her brain to release hormones that signal cells in her breast, called lactocytes, to rapidly increase the production of the complex mixture that makes up milk, which began with hormonal changes at the birth (**figure 2.5**). In response to the stimulus, information in certain genes is copied into molecules of **messenger RNA (mRNA)**, which then exit the nucleus (see steps 1 and 2 in figure 2.5). In the cytoplasm, the mRNAs, with the help of ribosomes and another type of RNA called **transfer RNA**, direct the manufacture of milk proteins. These include nutritive proteins called caseins, antibody proteins that protect against infection, and various enzymes.

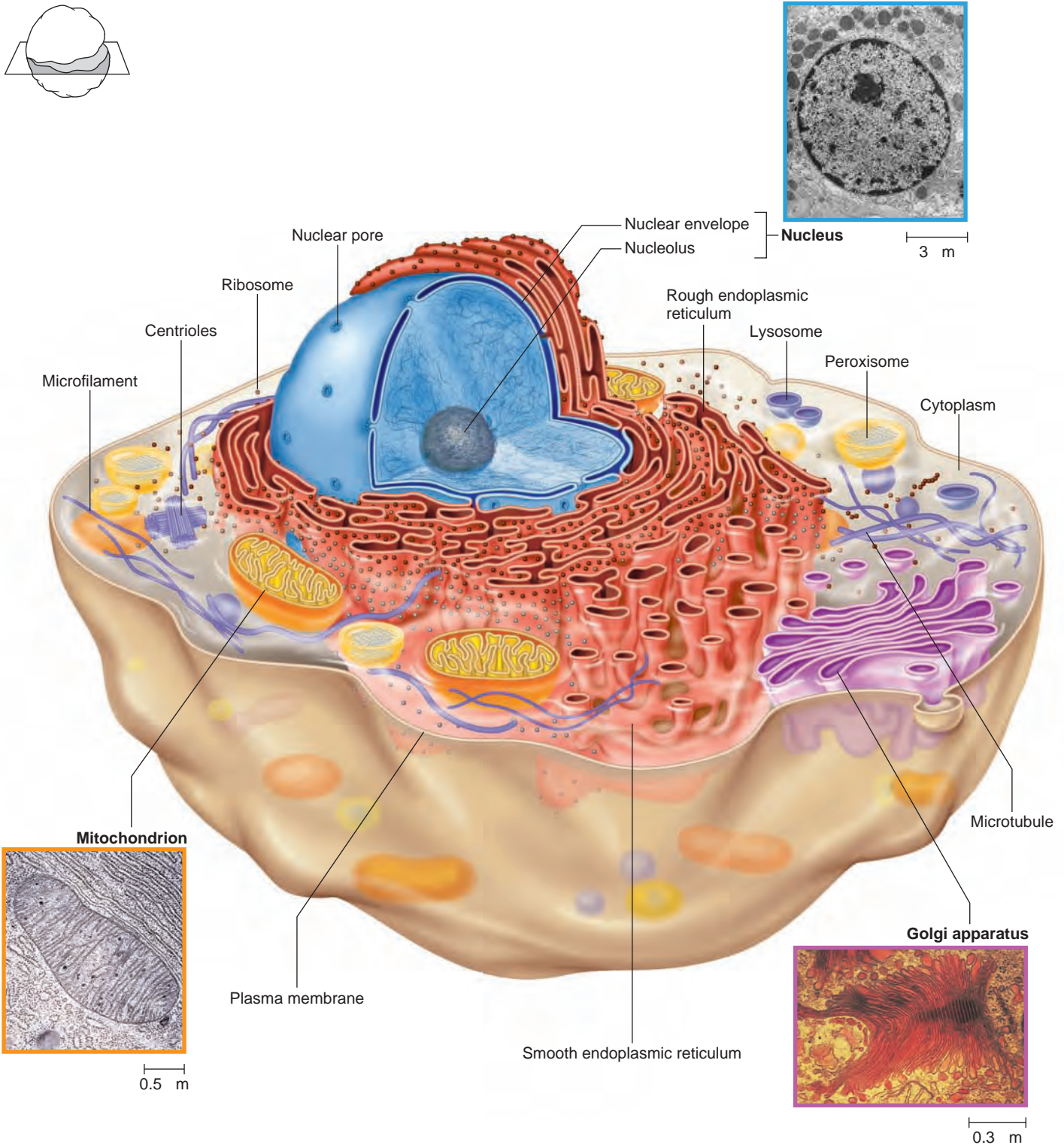
Most protein synthesis occurs on a maze of interconnected membranous tubules and sacs called the **endoplasmic reticulum (ER)** (see step 3 in figure 2.5). The ER winds from the nuclear envelope outward to the plasma membrane. The portion of the ER nearest the nucleus, which is flattened and studded with ribosomes, is called the rough ER because the ribosomes make it appear fuzzy when viewed under an electron microscope. Messenger RNA attaches to the ribosomes on the rough ER. Amino acids from the cytoplasm are then linked, following the instructions in the mRNA’s sequence, to form particular proteins that will either exit the cell or become part of membranes (step 3, figure 2.5). Proteins are also synthesized on ribosomes not associated with the ER. These proteins remain in the cytoplasm.

The ER acts as a quality control center for the cell. Its chemical environment enables the forming protein to start folding into the three-dimensional shape necessary for its specific function. Misfolded proteins are pulled out of the ER and degraded, much as an obviously defective toy might be pulled from an assembly line at a toy factory and discarded. Misfolded proteins that are not destroyed can cause disease, as discussed further in chapter 10.

As the rough ER winds out toward the plasma membrane, the ribosomes become

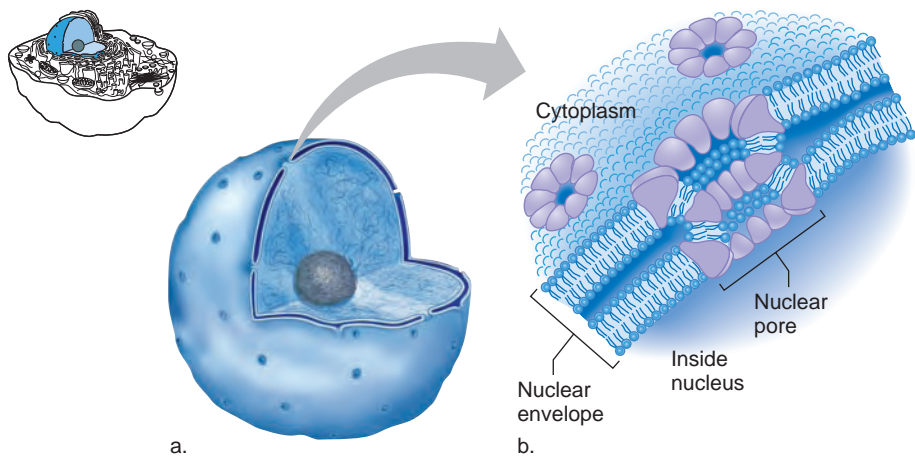


**Figure 2.2 Eukaryotic and prokaryotic cells.** A human cell is eukaryotic and much more complex than a bacterial cell, while an archaean cell looks much like a bacterial cell. Here, human macrophages (blue) capture bacteria (yellow). Note how much larger the human cells are. Yet a few types of giant bacteria are larger than some of the smaller human cell types.



**Figure 2.3 Generalized animal cell.** Organelles provide specialized functions for the cell. Most of these structures are transparent; colors are used here to distinguish them. Different cell types have different numbers of organelles. All cell types have a single nucleus, except for red blood cells, which expel their nuclei as they mature. Certain white blood cells have multilobed nuclei.

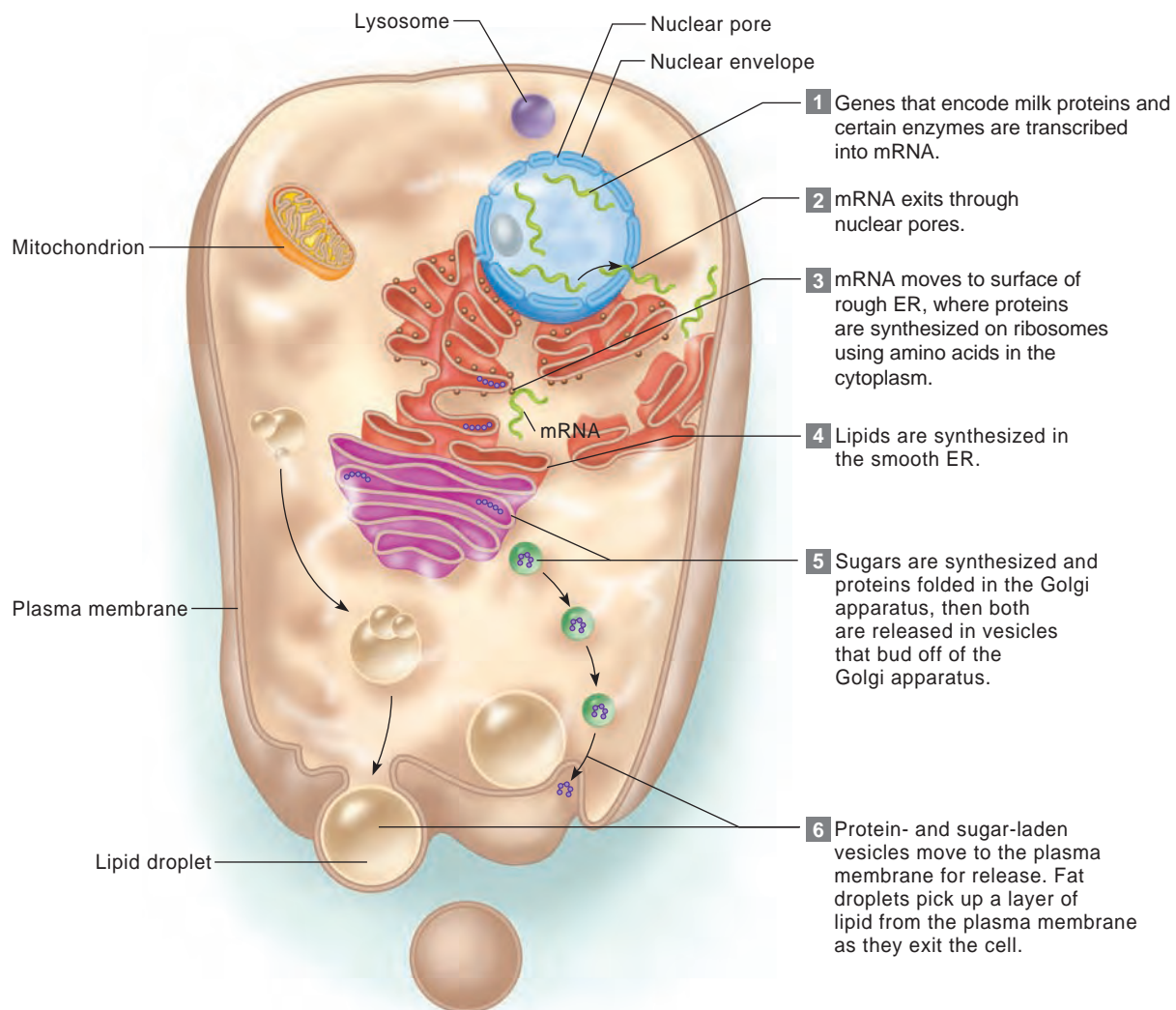




**Figure 2.4 The nucleus is the genetic headquarters.** (a) The largest structure in a typical human cell, the nucleus lies within two membrane layers that make up the nuclear envelope (b). Nuclear pores allow specific molecules to move in and out of the nucleus through the envelope.

fewer, and the tubules widen, forming a section called smooth ER. Here, lipids are made and added to the proteins arriving from the rough ER (step 4, figure 2.5). The lipids and proteins are transported until the tubules of the smooth ER eventually narrow and end. Then the proteins exit the ER in membrane-bounded, saclike organelles called **vesicles** that pinch off from the tubular endings of the membrane. Lipids are exported without a vesicle, because a vesicle is itself made of lipid.

A loaded vesicle takes its contents to the next stop in the secretory production line, the nearby **Golgi apparatus** (step 5, figure 2.5). This processing center is a stack of flat, membrane-enclosed sacs. Here, the milk sugar lactose is synthesized and other



**Figure 2.5 Secretion: Making milk.** Milk production and secretion illustrate organelle functions and interactions in a cell from a mammary gland: (1) through (6) indicate the order in which organelles participate in this process. Lipids are secreted in separate droplets from proteins and their attached sugars.

sugars are made that attach to proteins to form glycoproteins or to lipids to form glycolipids, which become parts of plasma membranes. Proteins finish folding in the Golgi apparatus.

The components of complex secretions, such as milk, are temporarily stored in the Golgi apparatus. Droplets of proteins and sugars then bud off in vesicles that move outward to the plasma membrane, fleetingly becoming part of the membrane until they are secreted to the cell's exterior. Lipids exit the plasma membrane directly, taking bits of it with them (step 6, figure 2.5).

Within the breast, epithelial cells called lactocytes form tubules, into which they secrete the components of milk. When the baby suckles, contractile cells squeeze the milk through the tubules and out of holes in the nipples. This “ejection reflex” is so powerful that the milk can actually shoot across a room!

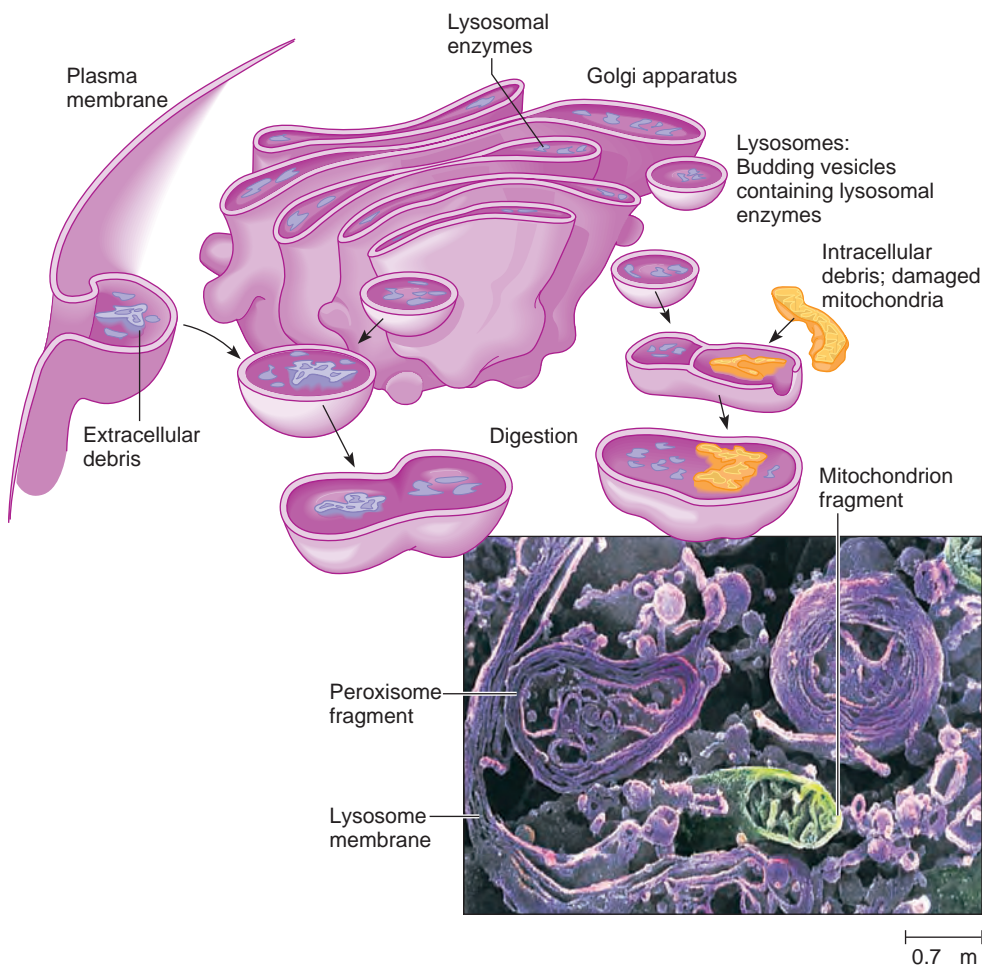
### Intracellular Digestion—Lysosomes and Peroxisomes

Just as clutter and garbage accumulate in an apartment, debris builds up in cells. Organelles called **lysosomes** handle the garbage. Lysosomes are membrane-bounded sacs that contain enzymes that dismantle bacterial remnants, worn-out organelles, and other debris (**figure 2.6**). The enzymes also break down some digested nutrients into forms that the cell can use.

Lysosomes fuse with vesicles carrying debris from outside or within the cell, and the lysosomal enzymes then degrade the contents. A loaded lysosome moves toward the plasma membrane and fuses with it, releasing its contents to the outside. The word *lysosome* means “body that lyses;” *lyse* means “to cut.” Lysosomes maintain the very acidic environment that their enzymes require to function, without harming other cellular constituents that could be destroyed by acid.

Cells differ in the number of lysosomes they contain. Certain white blood cells and macrophages that move about and engulf bacteria are loaded with lysosomes. Liver cells require many lysosomes to break down cholesterol, toxins, and drugs.

All lysosomes contain more than 40 types of digestive enzymes, which must be maintained in a correct balance. Absence or



**Figure 2.6 Lysosomes are trash centers.** Lysosomes fuse with vesicles or damaged organelles, activating the enzymes within to recycle the molecules. Lysosomal enzymes also dismantle bacterial remnants. These enzymes require a very acidic environment to function.

malfunction of an enzyme causes a “lysosomal storage disease.” In these inherited disorders, which are a type of inborn error of metabolism, the molecule that the missing or abnormal enzyme normally degrades accumulates. The lysosome swells, crowding organelles and interfering with the cell’s functions. In Tay-Sachs disease (OMIM 272800), for example, an enzyme that normally breaks down lipids in the cells that surround nerve cells is deficient. The nervous system becomes buried in lipid. An affected infant begins to lose skills at about six months of age, then gradually loses sight, hearing, and the ability to move, typically dying within three years. Even before birth, the lysosomes of affected cells swell.

**Peroxisomes** are sacs with outer membranes that are studded with several types of enzymes. These enzymes perform a variety of functions, including breaking down

certain lipids and rare biochemicals, synthesizing bile acids used in fat digestion, and detoxifying compounds that result from exposure to oxygen free radicals. Peroxisomes are large and abundant in liver and kidney cells.

The 1992 film *Lorenzo’s Oil* recounted the true story of a child with an inborn error of metabolism caused by an absent peroxisomal enzyme. Lorenzo had adrenoleukodystrophy (OMIM 202370), in which a type of lipid called a very-long-chain fatty acid builds up in the brain and spinal cord. Early symptoms include low blood sugar, skin darkening, muscle weakness, and irregular heartbeat. The patient eventually loses control over the limbs and usually dies within a few years. Eating a type of lipid in canola oil—the oil in the film’s title—slows buildup of the very-long-chain fatty acids in blood



plasma and the liver. But because the oil cannot enter the brain, it can only slow progression of the adrenoleukodystrophy. The disease can be cured, however, with a transplant of bone marrow stem cells from a compatible donor. In one family two young cousins with adrenoleukodystrophy had the transplant, but one died from the procedure, which is very risky. However, on autopsy all of his tissues were found to have the missing enzyme, which demonstrated, albeit tragically, that the stem cell transplant can correct the genetic problem.

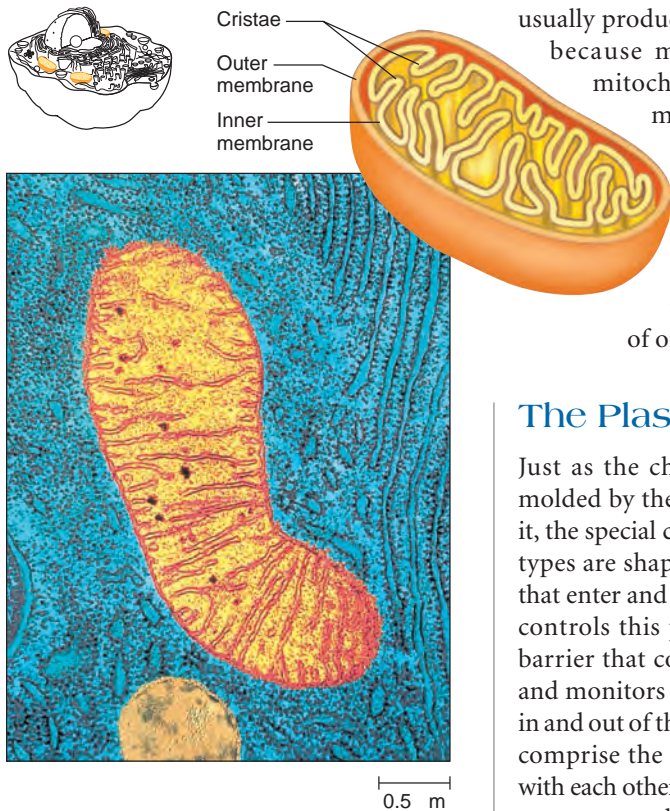
Energy Production—  
Mitochondria

The activities of secretion, as well as the many chemical reactions taking place in the cytoplasm, require continual energy. Organelles called **mitochondria** provide energy by breaking down nutrients from foods. The energy comes from the chemical bonds that hold together the nutrient molecules.

A mitochondrion has an outer membrane similar to those in the ER and Golgi apparatus and an inner membrane that forms folds called **cristae** (figure 2.7). These folds hold enzymes that catalyze the biochemical reactions that release energy from nutrient molecules. The energy liberated from food is captured and stored in the bonds that hold together a molecule called adenosine triphosphate (ATP). Therefore, ATP serves as a cellular energy currency.

The number of mitochondria in a cell varies from a few hundred to tens of thousands, depending upon the cell’s activity level. A typical liver cell, for example, has about 1,700 mitochondria, but a muscle cell, with its very high energy requirements, has many more.

Mitochondria are especially interesting because, like the nucleus, they contain DNA, although a very small amount. Another unusual characteristic of mitochondria is that they are almost always inherited from the mother only—mitochondria are located in the middle regions of sperm cells but usually not in the head regions that enter eggs. Moreover, rare mitochondria that do enter with a sperm are usually destroyed in the very early embryo. A class of inherited diseases whose symptoms result from abnormal mitochondria are characteristically passed from mother to offspring. These illnesses



**Figure 2.7 A mitochondrion extracts energy.** Cristae, infoldings of the inner membrane, increase the available surface area containing enzymes for energy reactions in a mitochondrion.

usually produce extreme muscle weakness, because muscle cells have so many mitochondria. Chapter 5 discusses mitochondrial inheritance, and chapter 15 describes how mitochondrial genes provide insights into early human migrations.

**Table 2.1** summarizes the structures and functions of organelles.

The Plasma Membrane

Just as the character of a community is molded by the people who enter and leave it, the special characteristics of different cell types are shaped in part by the substances that enter and leave. The plasma membrane controls this process. It forms a selective barrier that completely surrounds the cell and monitors the movements of molecules in and out of the cell. How the chemicals that comprise the plasma membrane associate with each other determines which substances can enter or leave the cell. Similar membranes form the outer boundaries of several organelles, and some organelles consist entirely of membranes. A cell’s membranes are more than mere coverings. Some of their

**Table 2.1**  
Structures and Functions of Organelles

Organelle	Structure	Function
Endoplasmic reticulum	Membrane network; rough ER has ribosomes, smooth ER does not	Site of protein synthesis and folding; lipid synthesis
Golgi apparatus	Stacks of membrane-enclosed sacs	Site where sugars are made and linked into starches or joined to lipids or proteins; proteins finish folding; secretions stored
Lysosome	Sac containing digestive enzymes	Degrades debris; recycles cell contents
Mitochondrion	Two membranes; inner membrane enzyme-studded	Releases energy from nutrients, participates in cell death
Nucleus	Porous sac containing DNA	Separates DNA from rest of cell
Peroxisome	Sac containing enzymes	Breaks down and detoxifies various molecules
Ribosome	Two associated globular subunits of RNA and protein	Scaffold and catalyst for protein synthesis
Vesicle	Membrane-bounded sac	Temporarily stores or transports substances



constituent or associated molecules carry out specific functions.

A biological membrane has a distinctive structure. It is built of a double layer (bilayer) of molecules called phospholipids. A phospholipid is a fat molecule with attached phosphate groups. It is often depicted as a head with two parallel tails. (A phosphate group  $[PO_4]$  is a phosphorus atom bonded to four oxygen atoms.) Membranes can form because phospholipid molecules self-assemble into sheets (figure 2.8). The

molecules do this because their ends react oppositely to water: The phosphate end of a phospholipid is attracted to water, and thus is hydrophilic (“water-loving”); the other end, which consists of two chains of fatty acids, moves away from water, and is therefore hydrophobic (“water-fearing”). Because of these forces, phospholipid molecules in water spontaneously form bilayers. Their hydrophilic surfaces are exposed to the watery exterior and interior of the cell, and their hydrophobic surfaces face each other on the inside of the bilayer, away from water.

A phospholipid bilayer forms the structural backbone of a biological membrane. Proteins are embedded in the bilayer. Some traverse the entire structure, while others extend from a face (figure 2.9).

Proteins, glycoproteins, and glycolipids extend from a plasma membrane. In this way they create surface topographies that are important in a cell’s interactions with other cells. The surfaces of your cells indicate that they are part of your body, and also that they have differentiated in a particular way.

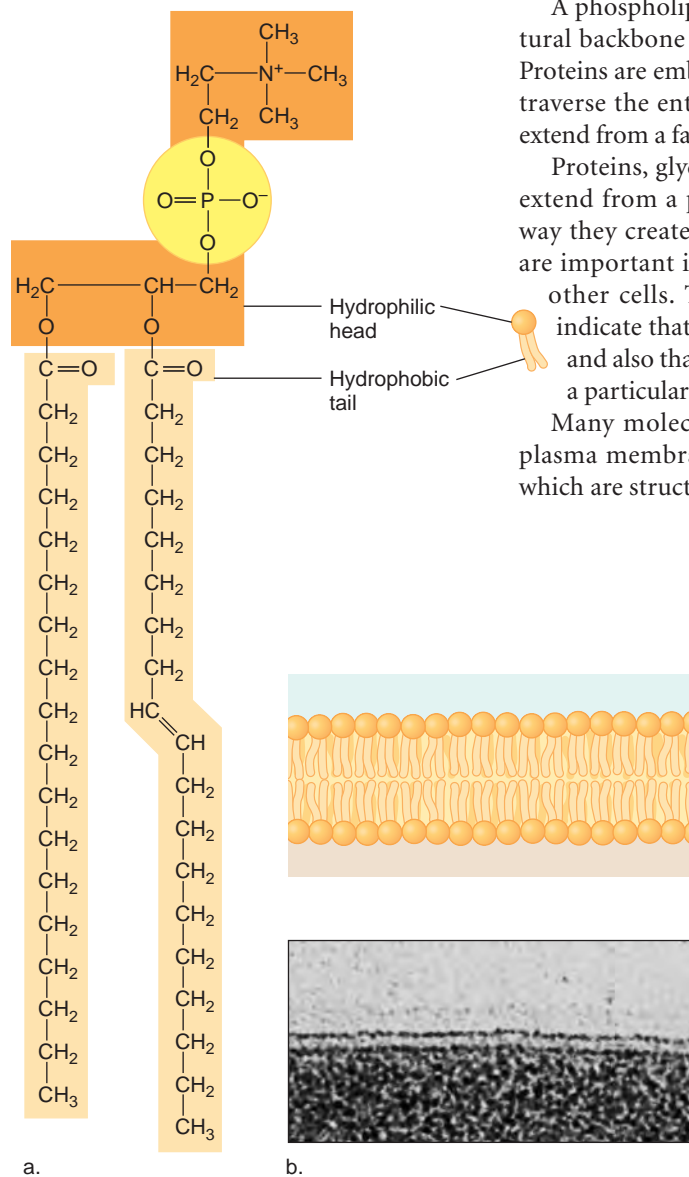
Many molecules that extend from the plasma membrane function as **receptors**, which are structures that have indentations

or other shapes that fit and hold molecules outside the cell. The molecule that binds to the receptor, called the **ligand**, may set into motion a cascade of chemical reactions that carries out a particular cellular activity, such as dividing.

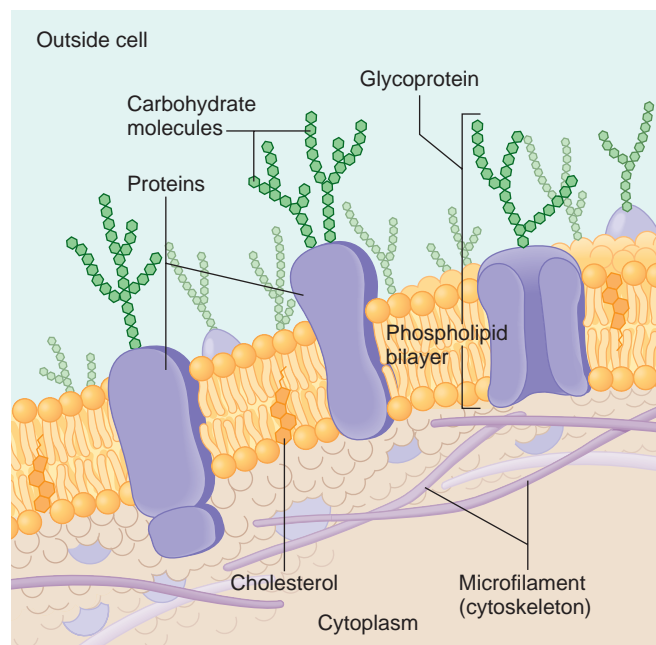
The phospholipid bilayer is oily, and some proteins move within it like ships on a sea. Proteins with related functions may cluster on “lipid rafts” that float on the phospholipid bilayer. The rafts are rich in cholesterol and other types of lipids. This clustering of proteins eases their interaction.

Proteins aboard lipid rafts have several functions. They contribute to the cell’s identity; act as transport shuttles into the cell; serve as gatekeepers; and can let in certain toxins and pathogens. HIV, for example, enters a cell by breaking a lipid raft.

The inner hydrophobic region of the phospholipid bilayer blocks entry and exit to most substances that dissolve in water. However, certain molecules can cross the membrane through proteins that form passageways, or when they are escorted by a “carrier” protein. Some membrane proteins form channels for ions (atoms or molecules with an electrical charge). **Reading 2.2** describes how faulty ion channels can cause disease.



**Figure 2.8 The two faces of membrane phospholipids.** (a) A phospholipid is literally a two-faced molecule, with one end attracted to water (hydrophilic, or “water-loving”) and the other repelled by it (hydrophobic, or “water-fearing”). A membrane phospholipid is often depicted as a circle with two tails. (b) An electron micrograph of a phospholipid bilayer.



**Figure 2.9 Anatomy of a plasma membrane.** In a plasma membrane, mobile proteins are embedded throughout a phospholipid bilayer. Other types of lipids aggregate to form “rafts,” and an underlying mesh of protein fibers provides support. Carbohydrates jut from the membrane’s outer face.

## Reading 2.2

# Faulty Ion Channels Cause Inherited Disease

What do abnormal pain intensity, irregular heartbeats, and cystic fibrosis have in common? All result from abnormal ion channels in plasma membranes.

Ion channels are protein-lined tunnels in the phospholipid bilayer of a biological membrane. These passageways permit electrical signals in the form of ions (charged particles) to pass through membranes.

Ion channels are specific for calcium ( $\text{Ca}^{+2}$ ), sodium ( $\text{Na}^{+}$ ), potassium ( $\text{K}^{+}$ ), or chloride ( $\text{Cl}^{-}$ ). A plasma membrane may have a few thousand ion channels for each of these ions. Ten million ions can pass through an ion channel in one second! The following disorders are a few that result from abnormal ion channels.

### Absent or Extreme Pain

The 10-year-old boy amazed the people on the streets of his small, northern Pakistani town. He was completely unable to feel pain, so he had become a performer, stabbing knives through his arms and walking on hot coals to entertain crowds. Several other people in this community where relatives often married relatives were also unable to feel pain. Researchers studied the connected families and discovered a mutation that alters sodium channels on certain nerve cells. The mutation blocks the channels so that the message to feel pain cannot be sent. The boy died at age 13 from jumping off a roof. His genes could protect him from pain, but pain protects against injury by providing a warning. He foolishly jumped.

A different mutation affecting the same sodium channel causes drastically different symptoms. In “burning man syndrome,”

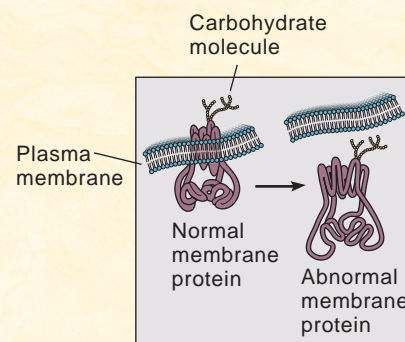
the channels become hypersensitive, opening and flooding the body with pain easily, in response to exercise, an increase in room temperature, or just putting on socks. In another condition, “paroxysmal extreme pain disorder,” the sodium channels stay open too long, causing excruciating pain in the rectum, jaw, and eyes. Researchers are using the information from studies of these genetic disorders to develop new painkillers.

### Long-QT Syndrome and Potassium Channels

Four children in a Norwegian family were born deaf, and three of them died at ages 4, 5, and 9. All of the children had inherited from unaffected carrier parents “long-QT syndrome associated with deafness” (OMIM 176261). (“QT” refers to part of a normal heart rhythm.) These children had abnormal potassium channels in the cells of the heart muscle and in the inner ear. In the heart cells, the malfunctioning ion channels disrupted electrical activity, fatally disturbing heart rhythm. In the cells of the inner ear, the abnormal ion channels increased the extracellular concentration of potassium ions, impairing hearing. Some cases of long-QT syndrome are caused not by faulty ion channels, but by proteins, called ankyrins, that anchor the channels in place within the plasma membrane.

### Cystic Fibrosis and Chloride Channels

A seventeenth-century English saying, “A child that is salty to taste will die shortly after birth,” described the consequence of



**Figure 1** In cystic fibrosis, CFTR protein remains in the cytoplasm, rather than anchoring in the plasma membrane. This prevents normal chloride channel function.

abnormal chloride channels in CF. The chloride channel is called CFTR, for cystic fibrosis transductance regulator. In most cases, CFTR protein remains in the cytoplasm, unable to reach the plasma membrane, where it would normally function (**Figure 1**). CF is inherited from carrier parents. The major symptoms of difficulty breathing, frequent severe respiratory infections, and a clogged pancreas that disrupts digestion all result from a buildup of extremely thick mucous secretions.

Abnormal chloride channels in cells lining the lung passageways and ducts of the pancreas cause the symptoms of CF. The primary defect in the chloride channels also disrupts sodium channels. The result: salt trapped inside cells draws moisture in and thickens surrounding mucus.

## The Cytoskeleton

The **cytoskeleton** is a meshwork of protein rods and tubules that molds the distinctive structures of a cell, positioning organelles and providing three-dimensional shape. The proteins of the cytoskeleton are continually broken down and built up as a cell performs specific activities. Some cytoskeletal

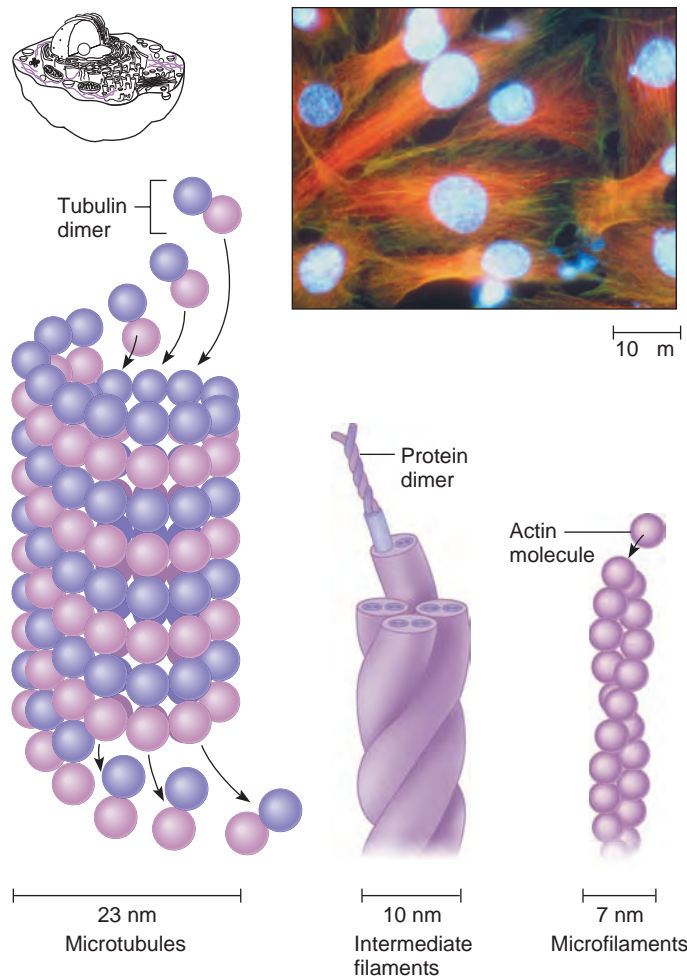
elements function as rails, forming conduits that transport cellular contents; other parts of the cytoskeleton, called motor molecules, power the movement of organelles along these rails by converting chemical energy to mechanical energy.

The cytoskeleton includes three major types of elements—**microtubules**, **microfilaments**, and **intermediate filaments**

(**figure 2.10**). They are distinguished by protein type, diameter, and how they aggregate into larger structures. Other proteins connect these components, creating the framework that provides the cell's strength and ability to resist force and maintain shape.

Long, hollow microtubules provide many cellular movements. A microtubule is composed of pairs (dimers) of a protein, called





**Figure 2.10 The cytoskeleton is made of protein rods and tubules.** The three major components of the cytoskeleton are microtubules, intermediate filaments, and microfilaments. Through special staining, the cytoskeletons in these cells appear orange under the microscope. (The abbreviation nm stands for nanometer, which is a billionth of a meter.)

tubulin, assembled into a hollow tube. The cell can change the length of the tubule by adding or removing tubulin molecules.

Cells contain both formed microtubules and individual tubulin molecules. When the cell requires microtubules to carry out a specific function—cell division, for example—the free tubulin dimers self-assemble into more tubules. After the cell divides, some of the microtubules fall apart into individual tubulin dimers. This replenishes the cell's supply of building blocks. Cells are perpetually building up and breaking down microtubules. Some drugs used to treat cancer affect the microtubules that pull a cell's duplicated chromosomes apart, either by preventing tubulin from assembling into microtubules, or by preventing

microtubules from breaking down into free tubulin dimers. In each case, cell division stops.

Microtubules also form cilia, which are hairlike structures. Coordinated movement of cilia generates a wave that moves the cell or propels substances along its surface. Cilia beat particles up and out of respiratory tubules, and cilia move egg cells in the female reproductive tract.

Another component of the cytoskeleton, the microfilaments, are long, thin rods composed of many molecules of the protein actin. Microfilaments are solid and narrower than microtubules. They enable cells to withstand stretching and compression. They also help to anchor one cell to another, and they provide many other functions

within the cell through proteins that interact with actin. When any of these proteins is absent or abnormal, a genetic disease results.

Intermediate filaments have diameters intermediate between those of microtubules and microfilaments, and are made of different proteins in different cell types. However, all intermediate filaments share a common overall organization of dimers entwined into nested coiled rods. Intermediate filaments are scarce in many cell types but are very abundant in cells of the skin.

The intermediate filaments in actively dividing skin cells in the bottommost layer of the epidermis (the upper skin layer) form a strong inner framework that firmly attaches the cells to each other and to the underlying tissue. These cellular attachments are crucial to the skin's barrier function. In a group of inherited conditions called epidermolysis bullosa (OMIM 226500, 226650, 131750), intermediate filaments are abnormal. The skin blisters easily as tissue layers separate.

Disruption of how the cytoskeleton interacts with other cell components can be devastating. Consider hereditary spherocytosis (OMIM 182900), which disturbs the interface between the plasma membrane and the cytoskeleton in red blood cells.

The doughnut shape of normal red blood cells enables them to squeeze through the narrowest blood vessels. Their cytoskeletons provide the ability to deform. Rods of a protein called spectrin form a meshwork beneath the plasma membrane, strengthening the red blood cell. Proteins called ankyrins attach the spectrin rods to the plasma membrane (**figure 2.11**). Spectrin molecules also attach to microfilaments and microtubules. Spectrin molecules are like steel girders, and ankyrins are like nuts and bolts. If either molecule is absent, the red blood cell cannot maintain its shape and collapses.

In hereditary spherocytosis, the ankyrins are abnormal, and parts of the red blood cell plasma membrane disintegrate, causing the cell to balloon out. The bloated cells obstruct narrow blood vessels—especially in the spleen, the organ that normally disposes of aged red blood cells. Anemia develops as the spleen destroys red blood cells more rapidly than the bone marrow can replace them. The result is great fatigue and weakness. Removing the spleen can treat the condition.



## Key Concepts

1. Cells are the units of life. They consist mostly of carbohydrates, lipids, proteins, and nucleic acids.
2. Organelles subdivide specific cell functions. They include the nucleus, the endoplasmic reticulum (ER), Golgi apparatus, mitochondria, lysosomes, and peroxisomes.
3. The plasma membrane is a flexible, selective phospholipid bilayer with embedded proteins and lipid rafts.
4. The cytoskeleton is an inner framework made of protein rods and tubules, connectors and motor molecules.

## 2.2 Cell Division and Death

A human body is built of about 100 trillion cells. About 10 trillion of them are replaced daily. For normal growth, repair, and development to occur, the cell numbers in a human body must be in balance. Mitotic cell division, or **mitosis**, provides new cells by forming two cells from one. Mitosis occurs in **somatic cells** (all cells but the sperm and eggs). Some cells must die as a body forms, just as a sculptor must take away some clay to shape the desired object. A foot, for example, starts out as a webbed triangle of tissue; toes emerge as certain cells die. This type of cell death, which is

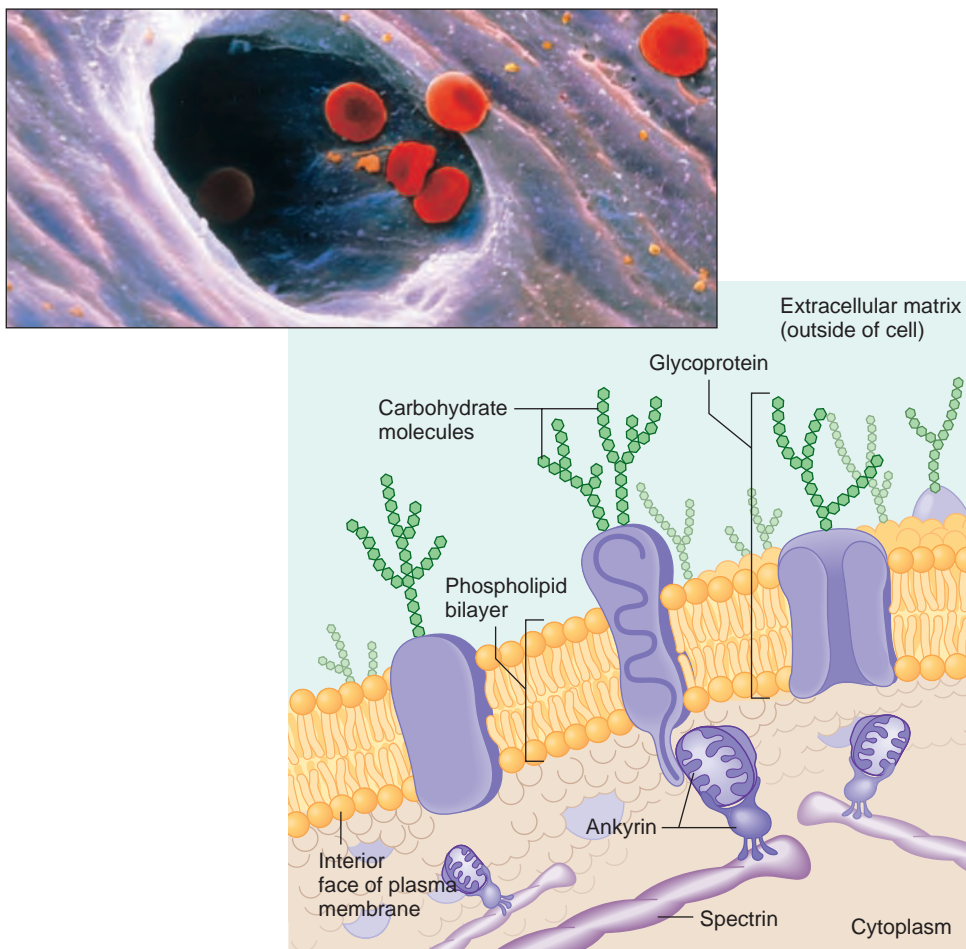
a normal part of development, is termed **apoptosis**, from the Greek for leaves falling from a tree. Apoptosis is a precise, genetically programmed sequence of events, as is mitosis (**figure 2.12**).

Another form of cell death, called necrosis, is a response to injury. It is not part of normal development. Yet another form of cell death occurs in the breasts of a pregnant woman, when fatty tissue shrinks and milk-secreting, glandular tissue grows.

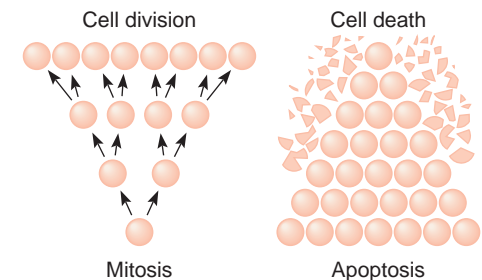
### The Cell Cycle

Many cell divisions transform a fertilized egg into a many-trillion-celled person. A series of events called the **cell cycle** describes the sequence of activities as a cell prepares for division and then divides.

Cell cycle rate varies in different tissues at different times. A cell lining the small intestine's inner wall may divide throughout life; a cell in the brain may never



**Figure 2.11 The red blood cell plasma membrane.** The cytoskeleton that supports the plasma membrane of a red blood cell withstands the turbulence of circulation. Proteins called ankyrins bind molecules of spectrin from the cytoskeleton to the inner membrane surface. On its other end, ankyrin binds proteins that help ferry molecules across the plasma membrane. In hereditary spherocytosis, abnormal ankyrin collapses the plasma membrane. The cell balloons—a problem for a cell whose function depends upon its shape. In the inset, normal red blood cells move from a large blood vessel into a smaller capillary. A red blood cell travels about 900 miles during its four-month existence. This is a falsely colored scanning electron micrograph (1,400 $\times$ ).



a.

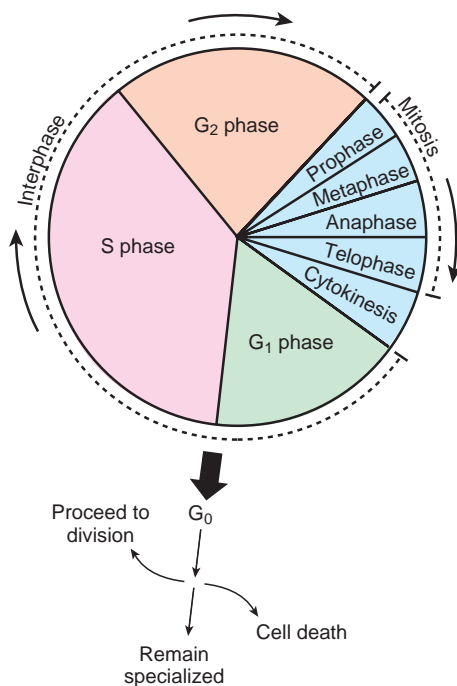


b.

**Figure 2.12 Mitosis and apoptosis mold a body.** Biological structures in animal bodies enlarge, allowing organisms to grow, as opposing processes regulate cell number. **(a)** Cell numbers increase from mitosis and decrease from apoptosis. **(b)** In the embryo, fingers and toes are carved from webbed structures. In syndactyly, normal apoptosis fails to carve digits, and webbing persists.

divide; a cell in the deepest skin layer of a 90-year-old may divide as long as the person lives. Frequent mitosis enables the embryo and fetus to grow rapidly. By birth, the mitotic rate slows dramatically. Later, mitosis maintains the numbers and positions of specialized cells in tissues and organs.

The cell cycle is continual, but we divide it into stages based on what we can observe. The two major stages are **interphase** (not dividing) and **mitosis** (dividing) (figure 2.13). In mitosis, a cell duplicates its chromosomes, then apportions one set into each of two resulting cells, called daughter cells. This maintains the set of 23 chromosome pairs characteristic of a human somatic cell. Another form of cell division, meiosis, produces sperm or eggs, which have half the amount of genetic material in somatic cells, or 23 single chromosomes. Chapter 3 discusses meiosis.



**Figure 2.13 The cell cycle.** The cell cycle is divided into interphase, when cellular components are replicated to prepare for division, and mitosis, when the cell splits, distributing its contents into two daughter cells. Interphase is divided into G<sub>1</sub> and G<sub>2</sub>, when the cell duplicates specific molecules and structures, and a phase S, when it replicates DNA. Mitosis is divided into four stages plus cytokinesis, when the cells separate. G<sub>0</sub> is a “time-out” when a cell “decides” which course of action to follow.

## Interphase—A Time of Great Activity

Interphase is a very active time. The cell continues the basic biochemical functions of life and also replicates its DNA and other subcellular structures. Interphase is divided into two gap (G<sub>1</sub> and G<sub>2</sub>) **phases** and one synthesis (S) **phase**. In addition, a cell can exit the cell cycle at G<sub>1</sub> to enter a quiescent phase called G<sub>0</sub>. A cell in G<sub>0</sub> maintains its specialized characteristics but does not replicate its DNA or divide. From G<sub>0</sub>, a cell may also proceed to mitosis and divide, or die. Apoptosis may ensue if the cell’s DNA is so damaged that cancer might result. G<sub>0</sub> then is when a cell’s fate is either decided or put on hold.

During G<sub>1</sub>, which follows mitosis, the cell resumes synthesis of proteins, lipids, and carbohydrates. These molecules will contribute to building the extra plasma membrane required to surround the two new cells that form from the original one. G<sub>1</sub> is the period of the cell cycle that varies the most in duration among different cell types. Slowly dividing cells, such as those in the liver, may exit at G<sub>1</sub> and enter G<sub>0</sub>, where they remain for years. In contrast, the rapidly dividing cells in bone marrow speed through G<sub>1</sub> in 16 to 24 hours. Cells of the early embryo may skip G<sub>1</sub> entirely.

During S phase, the cell replicates its entire genome. As a result, each chromosome then consists of two copies joined at an area called the **centromere**. In most human cells, S phase takes 8 to 10 hours. Many proteins are also synthesized during this phase, including those that form the mitotic **spindle** that will pull the chromosomes apart. Microtubules form structures called **centrioles** near the nucleus. Centriole microtubules are oriented at right angles to each other, forming paired oblong structures that organize other microtubules into the spindle.

G<sub>2</sub> occurs after the DNA has been replicated but before mitosis begins. More proteins are synthesized during this phase. Membranes are assembled from molecules made during G<sub>1</sub> and are stored as small, empty vesicles beneath the plasma membrane. These vesicles will merge with the plasma membrane to enclose the two daughter cells.

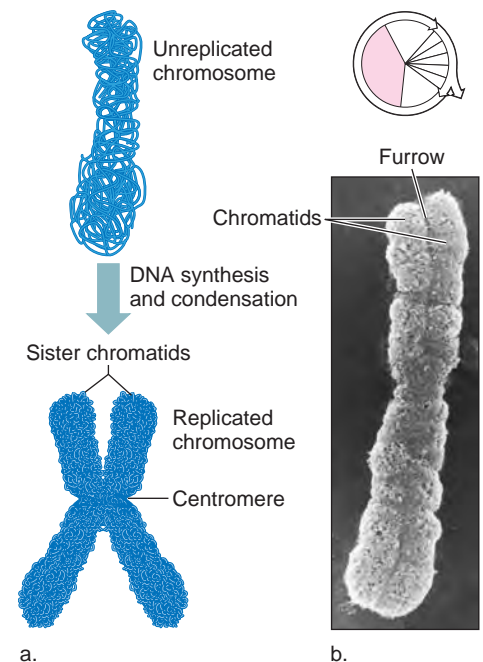
## Mitosis—The Cell Divides

As mitosis begins, the replicated chromosomes are condensed enough to be visible,

when stained, under a microscope. The two long strands of identical chromosomal material in a replicated chromosome are called **chromatids** (figure 2.14). At a certain point during mitosis, a replicated chromosome’s centromere splits, allowing its chromatid pair to separate into two individual chromosomes. (Although the centromere of a replicated chromosome appears as a constriction, its DNA is replicated.)

During **prophase**, the first stage of mitosis, DNA coils tightly. This shortens and thickens the chromosomes, which enables them to more easily separate (figure 2.15). Microtubules assemble from tubulin building blocks in the cytoplasm to form the spindles. Toward the end of prophase, the nuclear membrane breaks down. The nucleolus is no longer visible.

**Metaphase** follows prophase. Chromosomes attach to the spindle at their centromeres and align along the center of the cell, which is called the equator. Metaphase chromosomes are under great tension, but they appear motionless because they are pulled with equal force on both sides, like a tug-of-war rope pulled taut.



**Figure 2.14 Replicated and unreplicated chromosomes.** Chromosomes are replicated during S phase, before mitosis begins. Two genetically identical chromatids of a replicated chromosome join at the centromere (a). In the photograph (b), a human chromosome is forming two chromatids.

Next, during **anaphase**, the plasma membrane indents at the center, where the metaphase chromosomes line up. A band of microfilaments forms on the inside face of the plasma membrane, constricting the cell down the middle. Then the centromeres part, which relieves the tension and releases one chromatid from each pair to move to opposite ends of the cell—like a tug-of-war rope breaking in the middle and the participants falling into two groups. Microtubule movements stretch the dividing cell. During the very brief anaphase stage, a cell temporarily contains twice the normal number of chromosomes because each chromatid becomes an independently moving chromosome, but the cell has not yet physically divided.

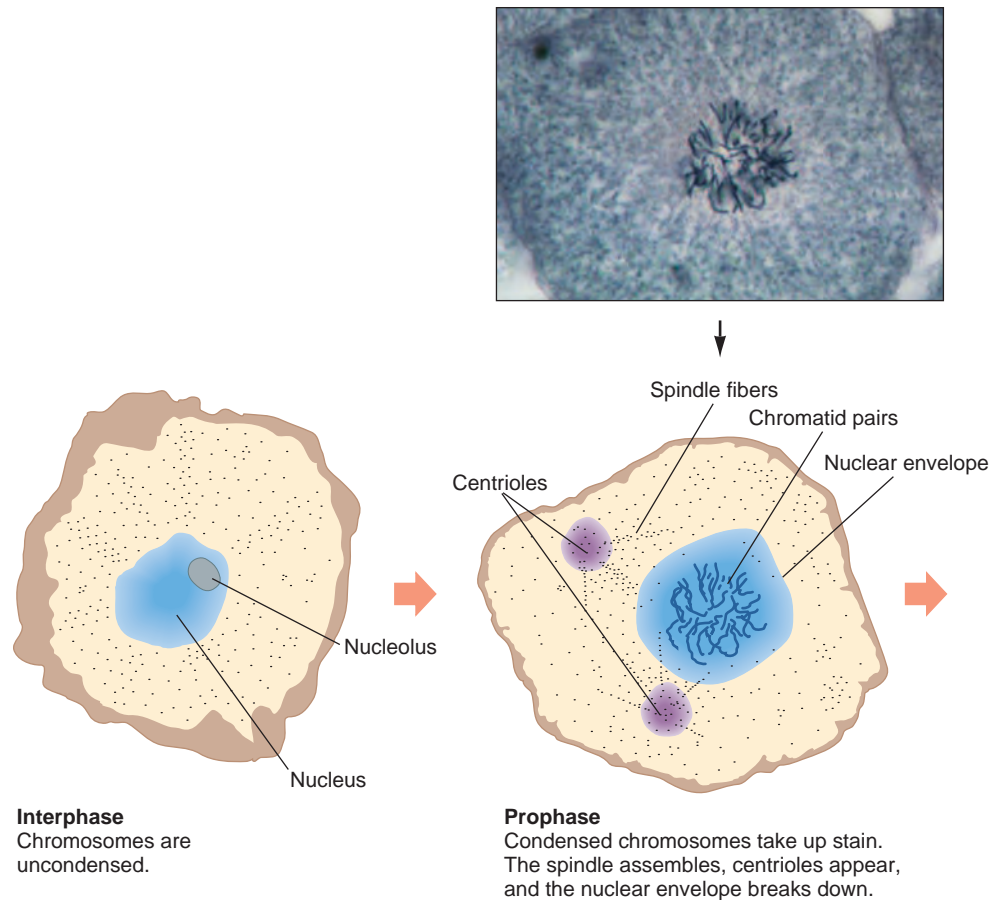
In **telophase**, the final stage of mitosis, the cell looks like a dumbbell with a set of chromosomes at each end. The spindle falls apart, and nucleoli and the membranes around the nuclei re-form at each end of the elongated cell. Division of the genetic material is now complete. Next, during **cytokinesis**, organelles and macromolecules are distributed between the two daughter cells. Finally, the microfilament band contracts like a drawstring, separating the newly formed cells.

## Control of the Cell Cycle

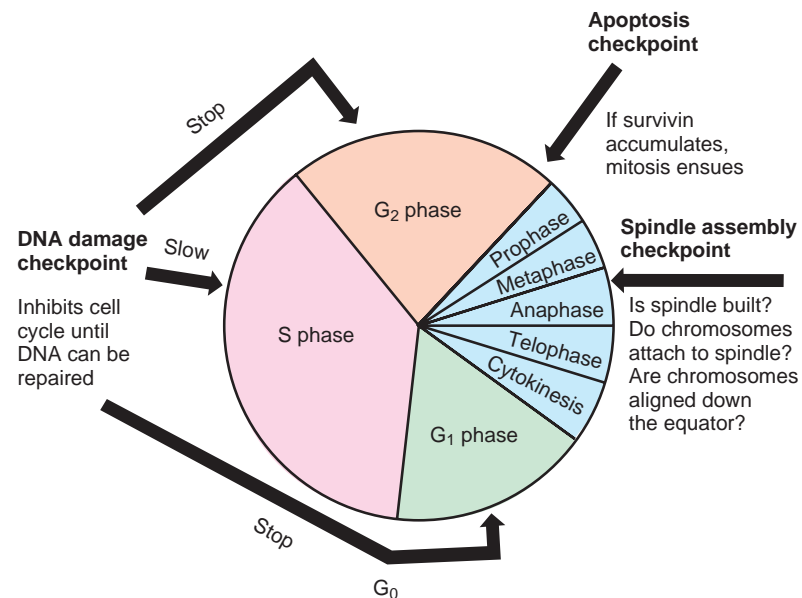
When and where a somatic cell divides is crucial to health. Illness can result from abnormally regulated mitosis. Control of mitosis is a daunting task. Quadrillions of mitoses occur in a lifetime, and not at random. Too little mitosis, and an injury goes unrepaired; too much, and an abnormal growth forms.

Groups of interacting proteins function at times in the cell cycle called checkpoints to ensure that chromosomes are faithfully replicated and apportioned into daughter cells (**figure 2.16**). A “DNA damage checkpoint,” for example, temporarily pauses the cell cycle while special proteins repair damaged DNA. An “apoptosis checkpoint” turns on as mitosis begins. During this checkpoint, proteins called survivins override signals telling the cell to die, ensuring that mitosis (division) rather than apoptosis (death) occurs. Later during mitosis, the “spindle assembly checkpoint” oversees construction of the spindle and the binding of chromosomes to it.

Cells obey an internal “clock” that tells them approximately how many times to divide. Mammalian cells grown (cultured) in a dish divide about 40 to 60 times. The

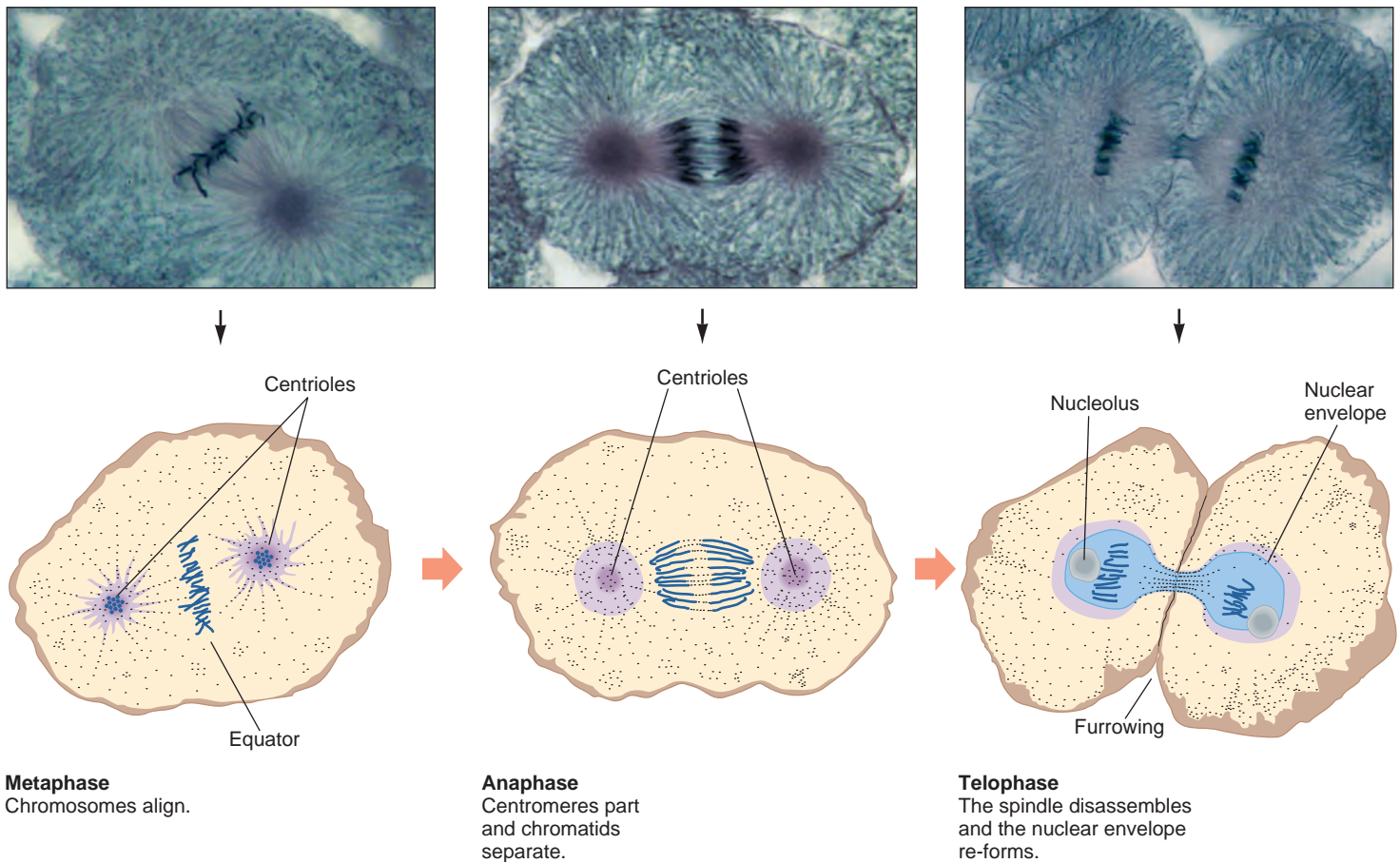


**Figure 2.15 Mitosis in a human cell.** Replicated chromosomes separate and are distributed into two cells from one. In a separate process, cytokinesis, the cytoplasm and other cellular structures distribute and pinch off into two daughter cells. (For simplicity, the chromosome pairs are represented schematically.)



**Figure 2.16 Cell cycle checkpoints.** Checkpoints ensure that mitotic events occur in the correct sequence. Many types of cancer result from faulty checkpoints.





mitotic clock ticks down with time. A connective tissue cell from a fetus, for example, will ultimately divide about 50 times. But a similar cell from an adult divides only 14 to 29 more times.

How can a cell “know” how many divisions remain? The answer lies in the chromosome tips, called **telomeres** (figure 2.17). Telomeres function like a cellular fuse that burns down as pieces are lost from the ends. Telomeres consist of hundreds to thousands of repeats of a specific six DNA-base sequence. At each mitosis, the telomeres lose 50 to 200 endmost bases, gradually shortening the chromosome. After about 50 divisions, a critical length of telomere DNA is lost, which signals mitosis to stop. The cell may remain alive but not divide again, or it may die.

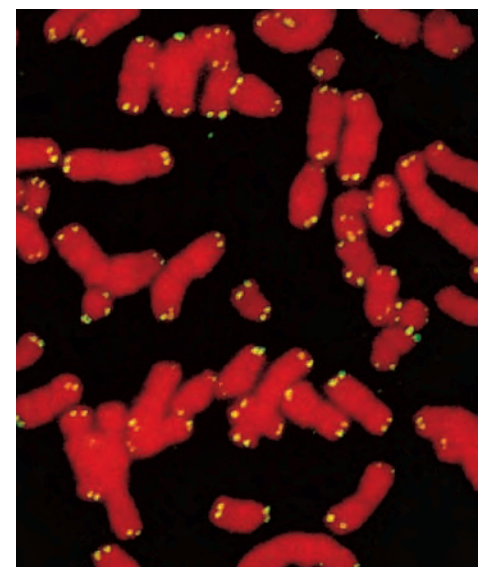
Not all cells have shortening telomeres. In eggs and sperm, in cancer cells, and in a few types of normal cells that must continually supply new cells (such as bone marrow cells), an enzyme called telomerase keeps chromosome tips long (see figure 18.3). However, most cells do not produce

telomerase, and their chromosomes gradually shrink. Chronic stress may hasten the shortening of telomeres.

Outside factors also affect a cell’s mitotic clock. Crowding can slow or halt mitosis. Normal cells growing in culture stop dividing when they form a one-cell-thick layer lining the container. This limitation to division is called contact inhibition. If the layer tears, the cells that border the tear grow and divide, filling in the gap. They stop dividing once the space is filled. Perhaps a similar mechanism in the body limits mitosis.

Chemical signals control the cell cycle from outside as well as from inside the cell. Hormones and growth factors are biochemicals from outside the cell that influence mitotic rate. A hormone is a substance synthesized in a gland and transported in the bloodstream to another part of the body, where it exerts a specific effect. Hormones secreted in the brain, for example, signal the cells lining a woman’s uterus to build up each month by mitosis in preparation

for possible pregnancy. Growth factors act more locally. Epidermal growth factor, for example, stimulates cell division in the skin beneath a scab.



**Figure 2.17 Telomeres.** Fluorescent tags mark the telomeres in this human cell.

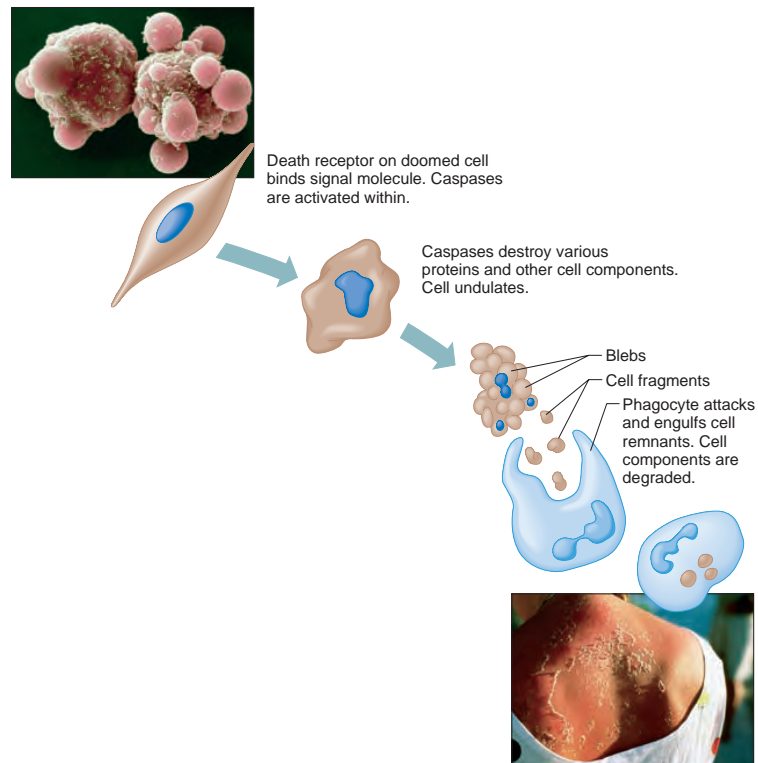
Two types of proteins, cyclins and kinases, interact inside cells to activate the genes whose products carry out mitosis. The two types of proteins form pairs. Cyclin levels fluctuate regularly throughout the cell cycle, while kinase levels stay the same. A certain number of cyclin-kinase pairs turn on the genes that trigger mitosis. Then, as mitosis begins, enzymes degrade the cyclin. The cycle starts again as cyclin begins to build up during the next interphase.

## Apoptosis

Apoptosis rapidly and neatly dismantles a cell into membrane-enclosed pieces that a phagocyte (a cell that engulfs and destroys another) can mop up. It is a little like taking the contents of a messy room and packaging them into garbage bags—then disposing of it all. In contrast is necrosis. This is a form of cell death associated with inflammation, rather than an orderly, contained destruction.

Like mitosis, apoptosis is a continuous, stepwise process. It begins when a “death receptor” on the doomed cell’s plasma membrane receives a signal to die. Within seconds, enzymes called caspases are activated inside the cell, stimulating each other and snipping apart various cell components. These killer enzymes:

- Demolish enzymes that replicate and repair DNA.
- Activate enzymes that cut DNA into similarly sized small pieces.
- Tear apart the cytoskeleton, including the cytoskeletal threads that support the nucleus, which collapses, condensing the DNA within.
- Cause mitochondria to release molecules that trigger further caspase activity, end the cell’s energy supply, and destroy these organelles.
- Abolish the cell’s ability to adhere to other cells.
- Send a certain phospholipid from the plasma membrane’s inner face to its outer surface. Here it attracts phagocytes that dismantle the cell remnants.



**Figure 2.18 Death of a cell.** A cell undergoing apoptosis loses its characteristic shape, forms blebs, and finally falls apart. Caspases destroy the cell’s insides. Phagocytes digest the remains. Note the blebs on the dying liver cells in the first photograph. Sunburn peeling is one example of apoptosis.

A dying cell has a characteristic appearance (**figure 2.18**). It rounds up as contacts with other cells are cut off, and the plasma membrane undulates, forming bulges called blebs. The nucleus bursts, releasing same-sized DNA pieces. Mitochondria decompose. Then the cell shatters. Almost instantly, pieces of membrane encapsulate the cell fragments, which prevents inflammation. Within an hour, the cell is gone.

From the embryo onward through development, mitosis and apoptosis are synchronized, so that tissue neither overgrows nor shrinks. In this way, a child’s liver retains much the same shape as she grows into adulthood. During early development, mitosis and apoptosis orchestrate the ebb and flow of cell number as new structures form. Later, these processes protect—mitosis produces new skin to heal a scraped knee; apoptosis peels away sunburnt skin cells that might otherwise become cancerous. Cancer is a profound derangement of the balance between cell division and death. In cancer, mitosis occurs too frequently or too many times, or apoptosis happens too infrequently. Chapter 18 discusses cancer in detail.

## Key Concepts

1. Mitosis and apoptosis regulate cell numbers during development, growth, and repair.
2. The cell cycle includes interphase and mitosis. During  $G_0$ , the cell “decides” to divide, die, or stay differentiated. Interphase includes two gap (G) phases and a synthesis (S) phase that prepares the cell for mitosis. During S phase, DNA is replicated. Proteins, carbohydrates, and lipids are synthesized during  $G_1$  and more proteins are synthesized in  $G_2$ . During prophase, metaphase, anaphase, and telophase, replicated chromosomes condense, align, split, and distribute into daughter cells.
3. The cell cycle is controlled by checkpoints; telomeres; hormones and growth factors from outside the cell; and cyclins and kinases from within.
4. During apoptosis, cells receive a death signal, activate caspases, and break apart in an orderly fashion.

## 2.3 Cell-Cell Interactions

Precisely coordinated biochemical steps orchestrate the cell-cell interactions that make multicellular life possible. Defects in cell communication and interaction cause certain inherited illnesses. Two broad types of interactions among cells are signal transduction and cellular adhesion.

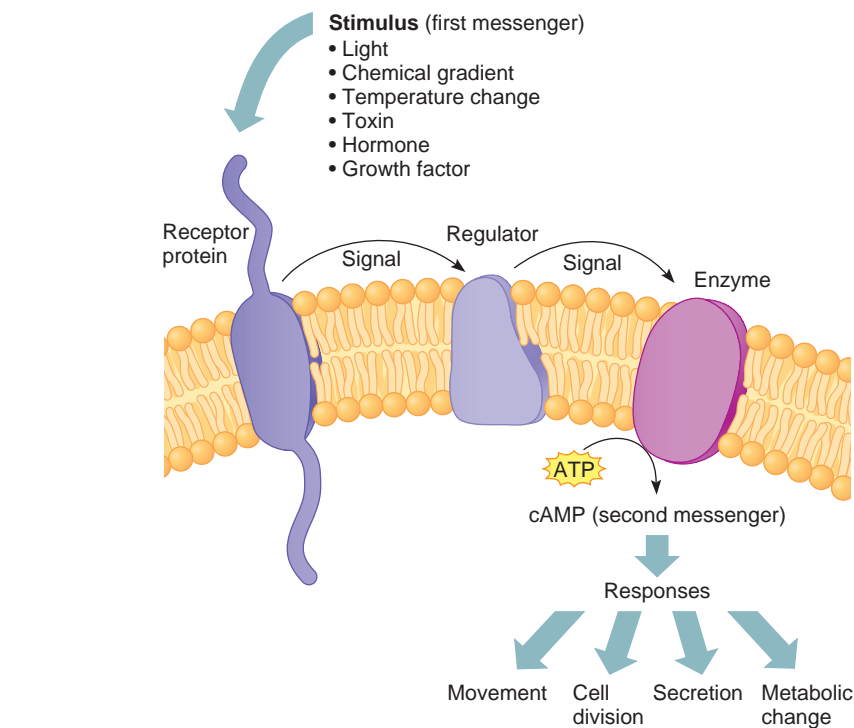
### Signal Transduction

In **signal transduction**, molecules on the plasma membrane assess, transmit, and amplify incoming messages to the cell's interior. *Transduce* means to change one form of something (such as energy or information) into another. In signal transduction, the cell changes various types of stimuli into specific biochemical reactions. A cell's existence may depend upon particular signal molecules binding receptors on the cell surface. Yet other signals must be ignored for cell survival, such as a signal to divide when cell division is not warranted. A cell's response to the many signals it receives is very complex.

The proteins that carry out signal transduction are in the cytoplasm and are embedded in the plasma membrane, from which they extend from one or both faces. They act in a sequence. The process begins at the cell surface. First, a receptor binds an incoming molecule, called the “first messenger.” The receptor then contorts, touching a nearby protein called a regulator (**figure 2.19**). Next, the regulator activates a nearby enzyme, which catalyzes (speeds) a specific chemical reaction. The product of this reaction, called the “second messenger,” is the key part of the entire process because it elicits the cell's response. This is usually activation of certain enzymes.

A single stimulus can trigger the production of many second messenger molecules. This is how signal transduction amplifies incoming information. Because cascades of proteins carry out signal transduction, it is a genetically controlled process.

Defects in signal transduction underlie many inherited disorders. In neurofibromatosis type 1 (NF1) (OMIM 162200), for example, tumors (usually benign) grow in nervous tissue, particularly under the skin. At the cellular level, NF1 occurs when cells



**Figure 2.19 Signal transduction.** A receptor binds a first messenger, triggering a cascade of biochemical activity at the cell's surface. An enzyme catalyzes a reaction inside the cell that circularizes ATP to cyclic AMP, the second messenger. cAMP then stimulates various responses, such as cell division, metabolic changes, and muscle contraction. Splitting ATP also releases energy.

fail to block transmission of a growth factor signal that triggers cell division. Affected cells misinterpret the signal and divide when it is inappropriate.

### Cellular Adhesion

**Cellular adhesion** is a precise sequence of interactions among the proteins that connect cells. Inflammation—the painful, red swelling at a site of injury or infection—illustrates one type of cellular adhesion. Inflammation occurs when white blood cells (leukocytes) move in the circulation to the injured or infected body part. There they squeeze between cells of the blood vessel walls to exit the circulation and reach the injury site. Cellular adhesion molecules, or CAMs, help guide white blood cells to the injured area.

Three types of CAMs carry out the inflammatory response: selectins, integrins, and adhesion receptor proteins (**figure 2.20**). First, selectins attach to the white blood cells and slow them to a roll by also binding to carbohydrates on the capillary wall.

(This is a little like putting out your arms to slow your ride down a slide.) Next, clotting blood, bacteria, or decaying tissues release chemical attractants that signal white blood cells to stop. The chemical attractants activate CAMs called integrins, which latch onto the white blood cells, and CAMs called adhesion receptor proteins, which extend from the capillary wall at the injury site. The integrins and adhesion receptor proteins then guide the white blood cells between the tile like lining cells to the injury site.

If the signals that direct white blood cells to injury sites fail, a condition called leukocyte-adhesion deficiency (OMIM 116920) results. The first symptom is often teething sores that do not heal. These and other small wounds never accumulate the pus (bacteria, cellular debris, and white blood cells) that indicates the body is fighting infection. The person lacks the CAMs that enable white blood cells to stick to blood vessel walls, and so blood cells travel right past wounds. An affected individual must avoid injury and infection, and receive anti-infective treatments for even the slightest wound.



More common disorders may also reflect abnormal cellular adhesion. Cancer cells journey easily from one part of the body to another thanks to impaired cellular adhesion. Arthritis may occur when the wrong adhesion molecules rein in white blood cells, inflaming a joint where no injury exists.

Cellular adhesion is critical to many other functions. CAMs guide cells surrounding an embryo to grow toward maternal cells and form the placenta, the supportive organ linking a pregnant woman to the fetus. Sequences of CAMs also help establish connections among nerve cells in the brain that underlie learning and memory.

## Key Concepts

1. In signal transduction, cell surface receptors receive information from first messengers (stimuli) and pass them to second messengers, which then trigger a cellular response.
2. Cellular adhesion molecules (CAMs) guide white blood cells to injury sites using a sequence of cell-protein interactions.

## 2.4 Stem Cells and Cell Specialization

Bodies grow and heal thanks to cells that retain the ability to divide, generating both new cells like themselves and cells that go on to specialize. **Stem cells** and **progenitor cells** renew tissues so that as the body grows, or loses cells to apoptosis, injury, and disease, other cells arise to take their places.

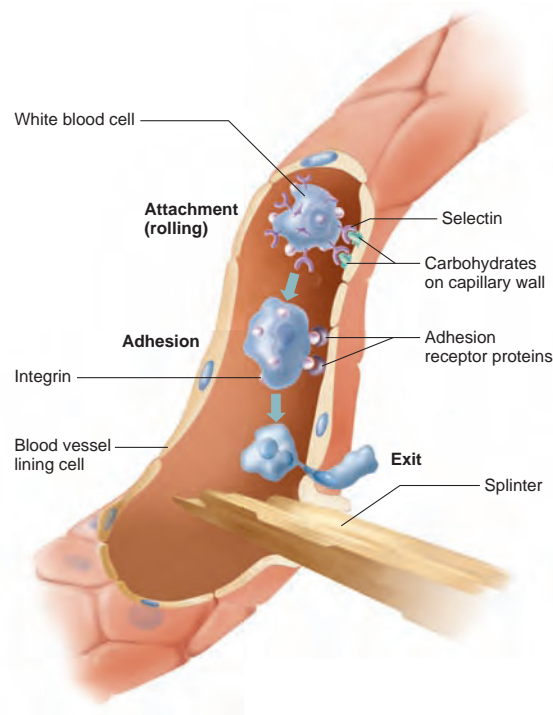
### Cell Lineages

A stem cell divides by mitosis to yield either two daughter cells that are stem cells like itself, or one that is a stem cell and one that is a partially specialized progenitor cell (**figure 2.21**). The characteristic of **self-renewal** is what makes a stem cell a stem cell—its ability to continue the lineage of cells that can divide to give rise to another cell like itself. A progenitor cell's daughters usually specialize as any of a restricted number of cell types. A fully differentiated cell, such as a mature blood cell, descends from a sequence of increasingly specialized pro-

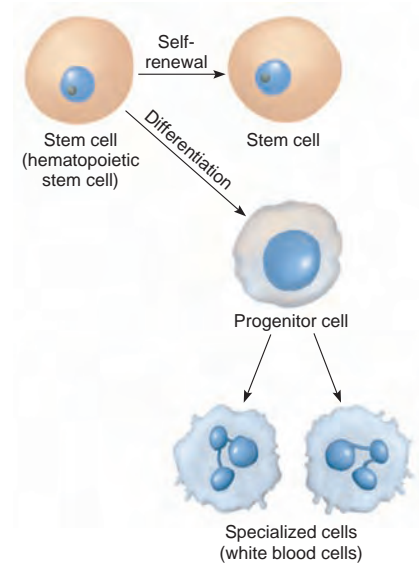
genitor cell intermediates, each one less like a stem cell and more like a blood cell. Our 260 or so differentiated cell types develop from lineages of stem and progenitor cells. **Figure 2.22** shows parts of a few lineages.

Stem cells and progenitor cells are described in terms of developmental potential—that is, according to the number of possible fates of their daughter cells. A fertilized ovum and the cells of the very early embryo, when it is just a small ball of identical-appearing cells, are totipotent. This means that they can give rise to every cell type. In contrast, stem cells that persist until later in development and progenitor cells are pluripotent: Their daughter cells have fewer possible fates. This is a little like a freshman's consideration of many majors, compared to a junior's more narrowed focus in selecting courses.

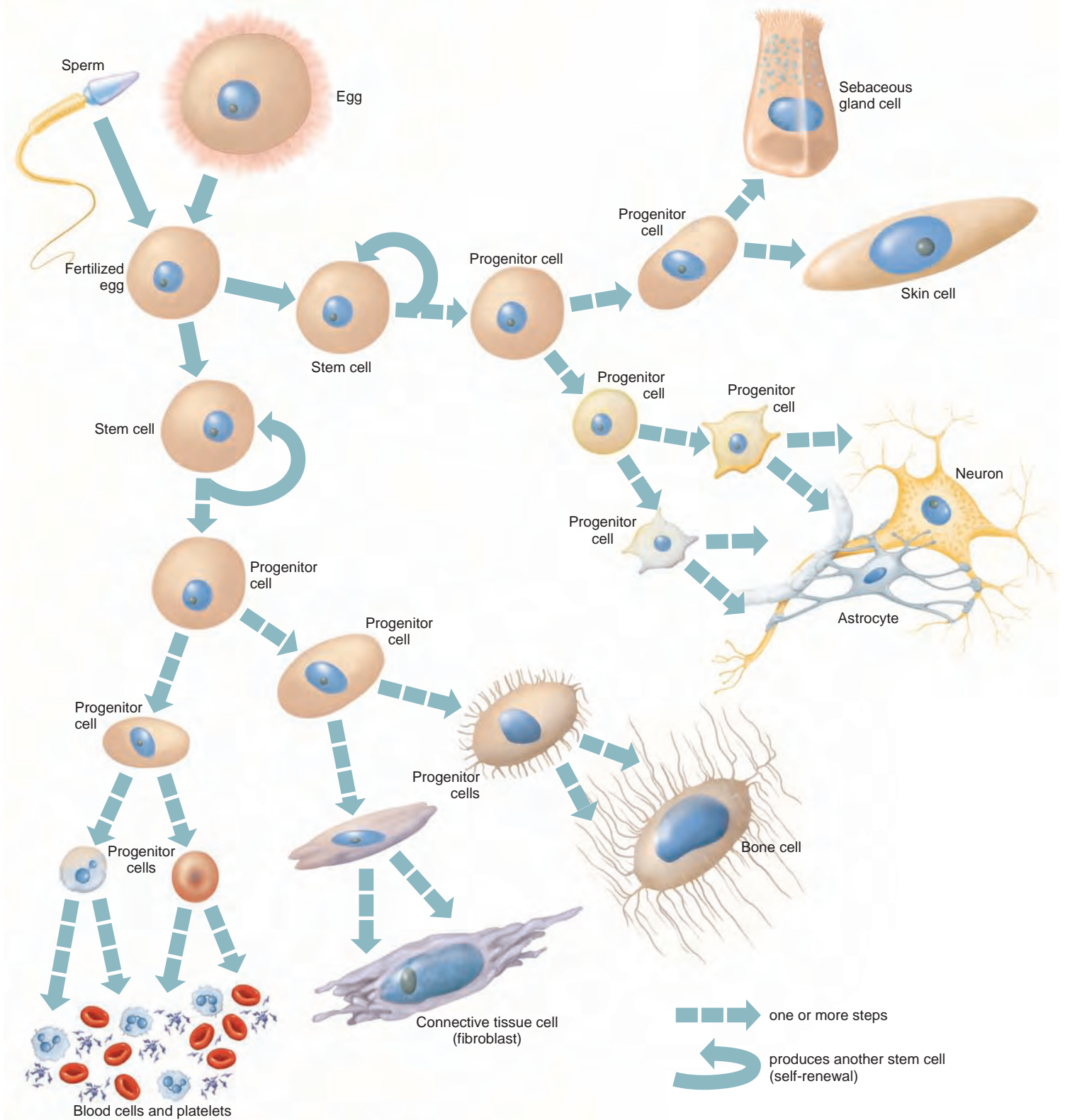
As stem cell descendants specialize, they express some genes and ignore others. An immature bone cell forms from a progenitor cell by manufacturing mineral-binding proteins and enzymes. In contrast, an immature muscle cell forms from a muscle progenitor cell that accumulates contractile proteins. The bone cell does not produce muscle proteins, nor does the



**Figure 2.20 Cellular adhesion.** Cellular adhesion molecules (CAMs), including selectins, integrins, and adhesion receptor proteins, direct white blood cells to injury sites.



**Figure 2.21 Stem cells and progenitor cells.** A stem cell is less specialized than the progenitor cell that descends from it by mitosis. Various types of stem cells provide the raw material for producing the specialized cells that comprise tissues, while retaining the ability to generate new cells. A hematopoietic stem cell resides in the bone marrow and can produce progenitors whose daughter cells may specialize as certain blood cell types.



**Figure 2.22 Pathways to cell specialization.** All cells in the human body descend from stem cells, through the processes of mitosis and differentiation. The differentiated cells on the lower left are all connective tissues (blood, connective tissue, and bone), but the blood cells are more closely related to each other than they are to the other two cell types. On the upper right, the skin and sebaceous gland cells share a recent progenitor, and both share a more distant progenitor with neurons and supportive astrocytes. Imagine how complex the illustration would be if it embraced all 260-plus types of cells in a human body!



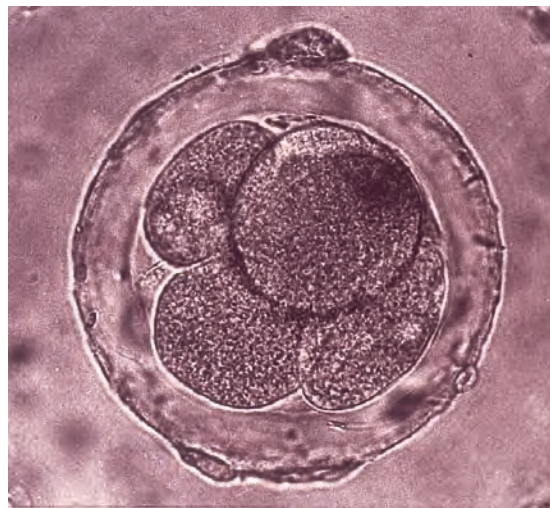
muscle cell produce bone proteins. All cells, however, synthesize proteins for basic “housekeeping” functions, such as energy acquisition and protein synthesis.

Many of the organs in an adult human body harbor stem or progenitor cells. These cells can divide when injury or illness occurs and generate new cells to replace damaged ones. Stem cells in the adult may have been set aside in the embryo or fetus in particular organs as repositories of future healing. Alternatively, or perhaps also, stem cells or progenitor cells may travel from the bone marrow to replace damaged or dead cells in response to signals that are released in injury or disease. Some stem and progenitor cells are quite versatile. For example, hematopoietic stem cells in bone marrow can form blood, nerve, muscle, liver, and blood vessel lining cells, under certain conditions. Because every cell contains all of an individual’s genetic material, it is theoretically possible that, given appropriate signals, any cell type can become any other. But this may only happen naturally under unusual conditions, such as catastrophic injury.

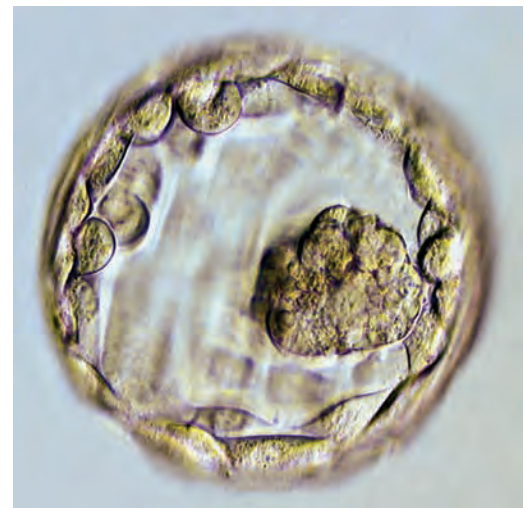
## Using Embryos

Physicians are beginning to use stem cells to treat particular disorders or injuries. Using stem cells to heal is one type of “regenerative medicine,” which replaces damaged tissue with materials that include cells that can divide.

Stem cells have several sources. They can be derived from the earliest embryos through the oldest elderly, and even from corpses and medical waste, such as tissue discarded after surgery. Theoretically, the most promising cells for therapy, because they can give rise to any cell type, are human embryonic stem (hES) cells. These are cultured from cells of an 8-celled embryo, or from a 5-day embryo, called a blastocyst. A blastocyst is a hollow ball of cells with a few cells, comprising a structure called the inner cell mass (ICM), on the inside. The



a. 8-celled human cleavage embryo



b. 5-day human blastocyst

**Figure 2.23** Human embryonic stem cells can be derived from 8-celled cleavage embryos (a) and 5-day blastocysts (b).

ICM develops into the embryo. **Figure 2.23** shows these two stages. In contrast, stem or progenitor cells in tissues can divide to give rise to fewer types of differentiated cells than can hES cells.

hES cells come from two sources. One is embryos from fertility clinics where couples undergoing *in vitro* (test tube) fertilization have frozen extra early embryos. This approach could create banks of cell types not precisely matched to a particular individual. “Typing” would have to be done, as it is for transfusions and transplants.

A second source of hES cells is to create an embryo using the nucleus from a somatic (body) cell from a patient, such as a person who has suffered a spinal cord injury (**figure 2.24**). This is called **somatic cell nuclear transfer** (SCNT) or simply nuclear transfer, and is sometimes called “cloning.” The nucleus is injected into or fused with a donated egg cell whose nucleus has been removed. The resulting cell—not a fertilized egg because no sperm is involved—develops until the 8-celled or blastocyst stage. Appropriate cells are removed and cultured to yield hES cells, then given growth factors to differentiate into needed cells and tissues—such as those that can patch a spinal cord injury.

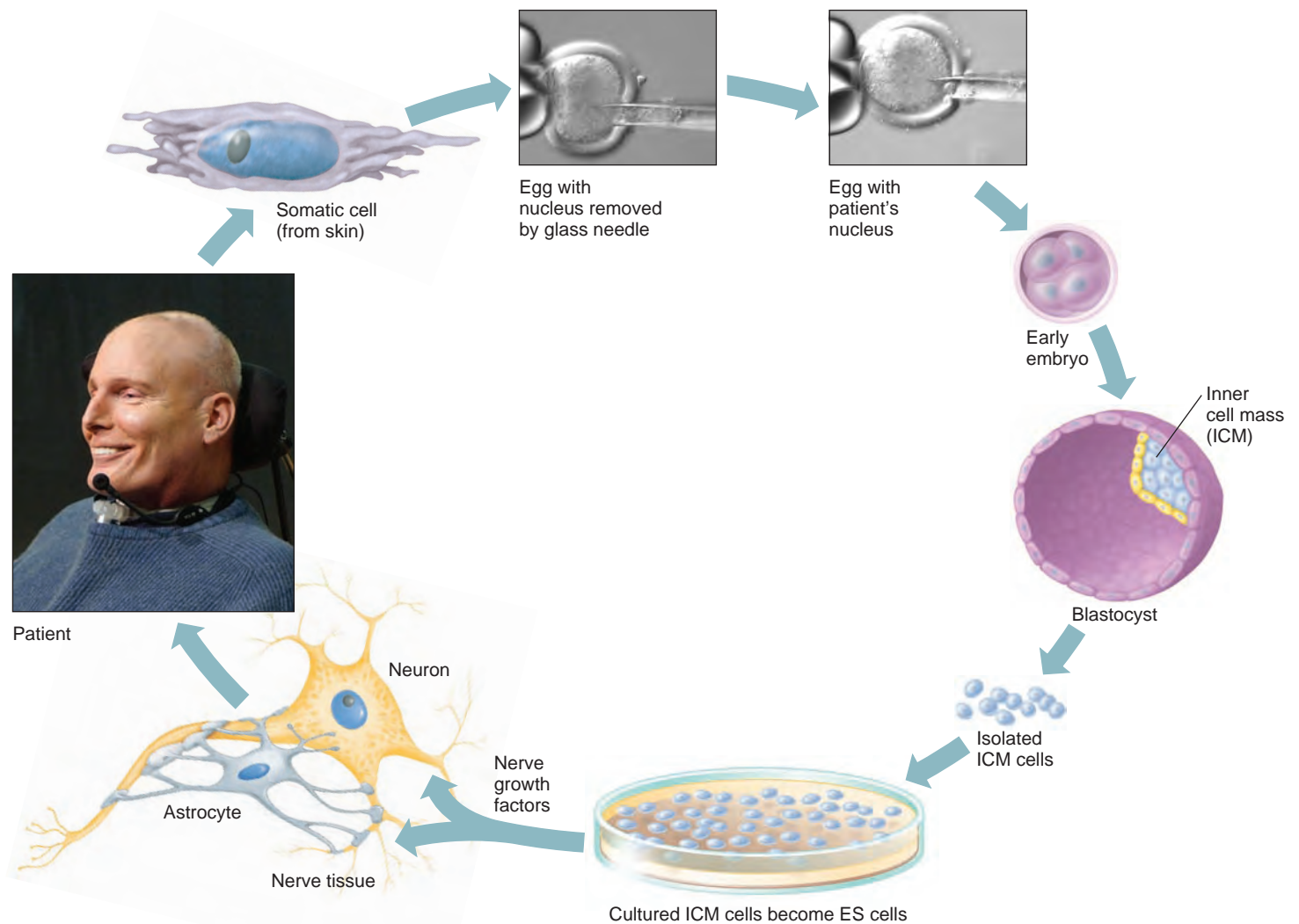
If researchers can learn how to guide stem cells to replace diseased or injured

tissues without overgrowing, the person’s body should accept them because they are a genetic match. This application is several years away because we do not understand exactly how cells interact to form organs. Stem cell therapies also face practical challenges, such as obtaining human eggs, the topic of the essay that begins chapter 3.

An application of SCNT that is likely to be used sooner than replacing body parts is to re-create a disease in a culture dish, so that the earliest abnormalities can be seen. Once researchers learn how a particular disease starts, they can screen collections of small molecules to identify potential new drugs. This approach might be very useful in developing treatments for diseases that do not produce symptoms until damage has already occurred at the cellular level, such as familial amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig’s disease) (OMIM 105400). By the time a person feels the initial symptoms of clumsiness or weakened muscles, many cells in the spinal cord have already died. Research using ES cells has changed the direction of familial ALS research by revealing that the initial abnormality is in astrocytes, not motor neurons, as had been thought.

Using hES cells derived from fertility clinic “leftovers” or SCNT is controversial. Some people object to using embryos





**Figure 2.24 Somatic cell nuclear transfer (SCNT) will yield embryonic stem cells genetically matched to a patient.**

A new way to possibly treat degenerative diseases and injuries is to culture cells whose nuclei come from a patient's own cells, and use the new cells to replace diseased or damaged cells. The immune system would not reject these cells, because they contain the patient's genome. An alternative approach to treat nervous system problems is to use neural stem cells taken from cadavers, but these would not match cells from the patient. The prospective patient in this illustration is the late actor Christopher Reeve, who had a spinal cord injury.

created to become children. Others maintain that the embryos—currently numbering half a million—are destined for discard anyway, so why not use their cells to help people who are already suffering? Some people object to SCNT because it creates an embryo with the intent to destroy it. Researchers counter that there are ways to obtain the cells without destroying the embryo, or they can use embryos that would not survive. It may even be possible to turn any cell into the equivalent of a hES cell by activating key “stemness” genes. Misunderstandings about the research can

stem from lack of knowledge about biology. For example, the stages of prenatal human development from which ES cells are derived do not have tissues or resemble a baby. Use of the word “cloning” also causes confusion. The intent of stem cell research is not to re-create a person, but to culture cells, a well-established technology.

Nations vary in their policies concerning research on human embryonic stem cells. Some permit both ways to obtain them (IVF leftovers and SCNT), some allow only one, and others ban or restrict government funding for either or both approaches.

## Using “Adult” Stem Cells

Less controversial than using human embryonic stem cells is to use so-called “adult” stem cells. These can be taken from individuals (not embryos or fetuses) without harming them. It is more accurate to call these cells “somatic,” “postnatal” or “non-embryonic” because they are also in embryos, fetuses, and newborns (especially in umbilical cord blood). Also, “adult” implies that these cells are only found in people old enough to vote!

Using non-embryonic stem cell implants is not new. Bone marrow transplants have delivered hematopoietic stem cells for half a century. Today, using stem cells from stored umbilical cord blood is routine in treating a variety of blood disorders.

Non-embryonic stem cells are not as potentially useful as hES cells, for several reasons.

- Truly pluripotent bone marrow cells might not exist. Researchers have been unable to isolate and identify them.
- Non-embryonic stem cells are restricted in the types of specialized cells that they can give rise to.
- Some organs might not have stem cells.

For these reasons, many biologists maintain that embryos are the most promising source of stem cells.

While the public debates the complex ethical issues surrounding stem cell research, biologists are very busy trying to understand how these cells function. In the

United States, much of this work is funded by private organizations, such as those that represent patients whose diseases could potentially be treated with stem cells. Some is conducted on cells from other species. Some researchers use the few “presidentially sanctioned” human embryonic stem cell lines, most of which are very abnormal genetically.

We still have much to learn about stem cells. What makes a stem cell a stem cell? Researchers have identified a set of about 80 genes that must be expressed to impart a state of “stemness” to a cell, many of which are involved in signal transduction. Because most of the genes are also expressed in non-stem cells, it appears that “stemness” arises from a combination of genes expressed at a particular time that are also expressed at other times and places, as well as from the actions of a few distinctive genes that appear to function only in stem cells. As analysis of the human genome continues, researchers will more precisely define the genetic functions that enable a cell to

retain developmental potential—essential to building and maintaining bodies, the subject of chapter 3.

## Key Concepts

1. All cells descend from progenitor and stem cells, most of which are pluripotent. The fertilized egg and cells of the early embryo are totipotent.
2. Differential gene expression underlies cell specialization.
3. Stem cells exist at all stages of development and throughout the body.
4. Embryonic stem cells are the most promising for regenerative medicine. They derive from fertilized ova stored at fertility clinics and from non-embryonic cell nuclear transfer.
5. Non-embryonic stem cells may have a variety of medical applications but have limitations compared to embryonic stem cells.

# Summary

## 2.1 The Components of Cells

1. Cells are the fundamental units of life and comprise the human body. Inherited traits and illnesses can be understood at the cellular and molecular levels.
2. All cells share certain features, but they are also specialized because they express different subsets of genes. Cells consist primarily of water and several types of macromolecules: **carbohydrates**, **lipids**, **proteins**, and **nucleic acids**.
3. The three domains of life—Archaea, Bacteria, and Eukarya—have characteristic cells. The archaea and bacteria are simple, small, and lack **nuclei** and other **organelles**. **Eukaryotic** cells have organelles, and their genetic material is contained in a nucleus.
4. Organelles sequester related biochemical reactions, improving the efficiency of life functions and protecting the cell. The cell also consists of **cytoplasm** and other chemicals.

5. The nucleus contains DNA and a nucleolus, which is a site of ribosome synthesis. **Ribosomes** provide scaffolds for protein synthesis; they exist free in the cytoplasm or complexed with the **rough endoplasmic reticulum (ER)**.
6. In secretion, the rough ER is the site of protein synthesis and folding, the **smooth ER** is the site of lipid synthesis, transport, and packaging, and the **Golgi apparatus** packages secretions into vesicles, which exit through the **plasma membrane**. **Lysosomes** contain enzymes that dismantle debris, and **peroxisomes** house enzymes that perform a variety of functions. Enzymes in **mitochondria** extract energy from nutrients.
7. The plasma membrane is a protein-studded phospholipid bilayer. It controls which substances exit and enter the cell, and how the cell interacts with other cells.
8. The **cytoskeleton** is a protein framework of hollow microtubules, made of tubulin, and solid microfilaments, which consist

of actin. Intermediate filaments are made of more than one protein type and are abundant in skin. The cytoskeleton and the plasma membrane distinguish different types of cells.

## 2.2 Cell Division and Death

9. Coordination of cell division (**mitosis**) and cell death (**apoptosis**) maintains cell numbers, enabling structures to enlarge during growth and development but preventing abnormal growth.
10. The **cell cycle** describes whether a cell is dividing (mitosis) or not (**interphase**). Interphase consists of two gap phases, when proteins and lipids are produced, and a synthesis phase, when DNA is replicated.
11. Mitosis proceeds in four stages. In **prophase**, replicated chromosomes consisting of two **chromatids** condense, the **spindle** assembles, the nuclear membrane breaks down, and the nucleolus is no longer visible. In **metaphase**, replicated chromosomes align along

the center of the cell. In **anaphase**, the **centromeres** part, equally dividing the now unreplicated chromosomes into two daughter cells. In **telophase**, the new cells separate. Cytokinesis apportions other components into daughter cells.

12. Internal and external factors control the cell cycle. Checkpoints are times when proteins regulate the cell cycle. **Telomere** (chromosome tip) length determines how many more mitoses will occur. Crowding, hormones, and growth factors signal cells from the outside; the interactions of cyclins and kinases trigger mitosis from inside.
13. In apoptosis, a receptor on the plasma membrane receives a death signal, then activates caspases that tear apart the cell in an orderly fashion. Membrane surrounds the pieces, preventing inflammation.

## 2.3 Cell-Cell Interactions

14. In **signal transduction**, a stimulus (first messenger) activates a cascade of action among membrane proteins, culminating in the production of a second messenger that turns on enzymes that provide the response.
15. **Cellular adhesion** molecules enable cells to interact. Selectins slow the movement of leukocytes, and integrins and adhesion receptor proteins guide the blood cell through a capillary wall to an injury site.

## 2.4 Stem Cells and Cell Specialization

16. **Stem cells** produce daughter cells that retain the ability to divide and daughter cells that specialize in particular ways.

17. Totipotent stem cells can become anything. Pluripotent stem cells can differentiate as any of a variety of cell types. **Progenitor cells** can specialize as any of a restricted number of cell types.
18. Human embryonic stem (hES) cells have more medical applications and are less likely to be rejected than stem cells from somatic tissues.
19. hES cells can be obtained from existing embryos (IVF “leftovers”) or be tailor-made (through **somatic cell nuclear transfer**).
20. Researchers are developing ways to use the body’s stem and progenitor cells to heal.

# Review Questions

1. Match each organelle to its function.
 

Organelle	Function	
a. lysosome	1. lipid synthesis	d. checkpoint proteins
b. rough ER	2. houses DNA	e. cellular adhesion molecules
c. nucleus	3. energy extraction	
d. smooth ER	4. dismantles debris	3. List four types of controls on cell cycle rate.
e. Golgi apparatus	5. detoxification	4. How can all of a person’s cells contain exactly the same genetic material, yet specialize as bone cells, nerve cells, muscle cells, and connective tissue cells?
f. mitochondrion	6. protein synthesis	5. Distinguish between
g. peroxisome	7. processes secretions	a. a bacterial cell and a eukaryotic cell.
2. Explain the functions of the following proteins:
  - a. tubulin and actin
  - b. caspases
  - c. cyclins and kinases
  - d. rough ER and smooth ER.
  - e. microtubules and microfilaments.
  - f. a stem cell and a progenitor cell.
  - g. totipotent and pluripotent.
6. Select a process described in the chapter (such as signal transduction or apoptosis). List the steps and state why the cell could not survive without this ability.
7. How are intermediate filaments similar to microtubules and microfilaments, and how are they different?
8. What advantage does compartmentalization provide to a large and complex cell?
9. What role does the plasma membrane play in signal transduction?
10. Explain how stem cells obtained from IVF leftovers and somatic cell nuclear transfer differ in terms of the sources of their genomes.

# Applied Questions

1. How might abnormalities in each of the following contribute to cancer?
  - a. cellular adhesion
  - b. signal transduction
  - c. balance between mitosis and apoptosis
  - d. cell cycle control
  - e. telomerase activity
2. Why do many inherited conditions result from defective enzymes?
3. In neuronal ceroid lipofuscinosis (OMIM 610127), a child experiences seizures, loss of vision, and lack of coordination, and dies. The body lacks an enzyme that normally breaks down certain proteins, causing them to accumulate and destroying the nervous system. Name two organelles that could be affected in this illness.
4. How do stem cells maintain their populations within tissues that consist of mostly differentiated cells?
5. Explain why mitosis that is too frequent or too infrequent, or apoptosis that is too frequent or too infrequent, can endanger health.
6. Why wouldn’t a cell in an embryo likely be in phase G<sub>0</sub>?
7. A defect in which organelle would cause fatigue?
8. Describe three ways that drugs can be used to treat cancer, based on disrupting



microtubule function, telomere length, and signal transduction.

9. How can signal transduction, the plasma membrane, and the cytoskeleton function together?
10. What abnormality at the cellular or molecular level lies behind each of the following disorders?
  - a. cystic fibrosis
  - b. adrenoleukodystrophy
  - c. neurofibromatosis type 1
  - d. leukocyte adhesion deficiency
  - e. syndactyly
11. A child with sickle cell disease (OMIM 603903) endures periods of crisis, when circulation becomes painfully poor, starving parts of the body of oxygen. The blood of a child in crisis contains many more stem cells, sent from the bone marrow, than does the blood of a child not in crisis. What does this suggest about stem cell function?
12. A single stem cell in skin gives rise to skin cells, hair follicle cells, and sebaceous (oil) gland cells. Suggest a treatment that might use these cells.
13. Researchers removed brain matter from a young woman who suffered from more than 100 seizures a day. The surgery helped her. The researchers then grew “adult human neural progenitor cells” from this brain material, which would otherwise have been discarded. Suggest one way that these cells might be used.
14. Who do you think should have input into whether or not federal funds are spent on establishing human hES cell lines? Explain your reason.
15. The thymus gland in the chest manufactures white blood cells that protect against infection. It begins to shrink in adolescence. Researchers have discovered that a single variety of stem cell can, in a dish, be stimulated to regrow a thymus. List the steps to use somatic cell nuclear transfer to create a thymus gland to help a person suffering from AIDS.

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 2** and **Web Activities** to find the website links needed to complete the following activities.

16. The Coalition for the Advancement of Medical Research includes scientists, foundations, and patients advocating stem cell research for regenerative medicine. Consult the website provided on the OLC to learn the latest news on legislative efforts to either ban or spare stem cell research,

and explain which types of research the bills would and would not allow.

17. Select ten nations and, using a web search engine, research whether they allow the use of IVF leftovers to obtain human ES cells, somatic cell nuclear transfer to obtain the cells, neither, or both.

### Case Studies and Research Results

18. Based on the idea that the bone marrow contains very rare pluripotent stem cells, some surgeons have been injecting samples of patient’s bone marrow into their hearts during cardiac bypass surgery. Even though such pluripotent cells had never been identified, the hypothesis was that they must be present. When patients recovered well, it looked like the stem cells were working. However, a large-scale long-term study eventually showed that patients who received their own bone marrow stem cells did better than patients who did not. Suggest another approach to using stem cells to heal hearts.
19. Studies show that women experiencing chronic stress, such as from caring for a severely disabled child, have telomeres that shorten at an accelerated rate. Suggest a study that would address the question of whether men have a similar reaction to chronic stress.

## A Second Look

1. Describe three types of cells mentioned in the chapter-opening case study.
2. How is signal transduction part of the healing that occurred in Michael M.’s eye and in the mice with retinitis pigmentosa?
3. Why was the stem cell treatment that restored Michael M.’s vision a more lasting cure than the treatment for retinitis pigmentosa in mice?



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Meiosis and Development

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- 3.2 **Meiosis**
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## SELLING EGGS: VANESSA'S STORY

"I couldn't believe the ad in the student newspaper—a semester's tuition for a few weeks of discomfort! So I applied. I was 18, on the volleyball team, healthy except for some acne, and had a 3.8 GPA. Since I didn't plan on having children at the time, or at all, I thought why not?"

I passed the physical and psychological screens, and my family history seemed OK. I was accepted! Then three weeks later, I got the call. A young couple who couldn't have a child because the woman had had cancer wanted to use donor eggs, to be fertilized *in vitro* by the man's sperm. They'd seen my photo and read my file, and thought I'd be a good match. I was thrilled, but the warnings scared me: bleeding, infection, cramping, mood swings, and scarred ovaries.

For the first 10 days, I gave myself shots in the thigh of a drug to suppress my ovaries. Then for the next 12 days, I injected myself with two other drugs in the back of the hip, to mature my egg cells. Frequent ultrasounds showed that my ovaries looked like grape clusters, with the maturing eggs popping to the surface. Towards the end I felt a dull aching in my belly.

The egg retrieval wasn't bad. I was sedated, had anesthesia, and the doctor removed 20 eggs using a needle passed through the wall of my vagina. My middle ached at night and the next day, and I felt bloated for a few days. But a dozen of my eggs were retrieved! The couple had two of them implanted, and the rest were frozen, for possible later use.

Where are they today, my two—or more?—biological children? I chose not to stay in touch with the couple, but now that I have children, sometimes I wonder."

**EGG  
DONORS  
WANTED**

**\$10,000 PLUS  
EXPENSES**

*Seeking young women (under 28) who are attractive, athletic, healthy, and with high SAT scores or GPAs.*

Genes orchestrate our physiology from a few days after conception through adulthood. As a result, malfunctions of genes affect people of all ages. Certain single-gene mutations act before birth, causing broken bones, dwarfism, or even cancer. Many other mutant genes exert their effects during childhood, and it may take parents months or even years to realize their child has a health problem. Duchenne muscular dystrophy (see figure 2.1), for example, usually begins as clumsiness in early childhood. Inherited forms of heart disease and breast cancer can appear in early or middle adulthood, which is earlier than multifactorial forms of these conditions. Pattern baldness is a very common inherited trait that may not become obvious until well into adulthood.

This chapter explores the stages of the human life cycle. Genes function against this developmental backdrop.

### 3.1 The Reproductive System

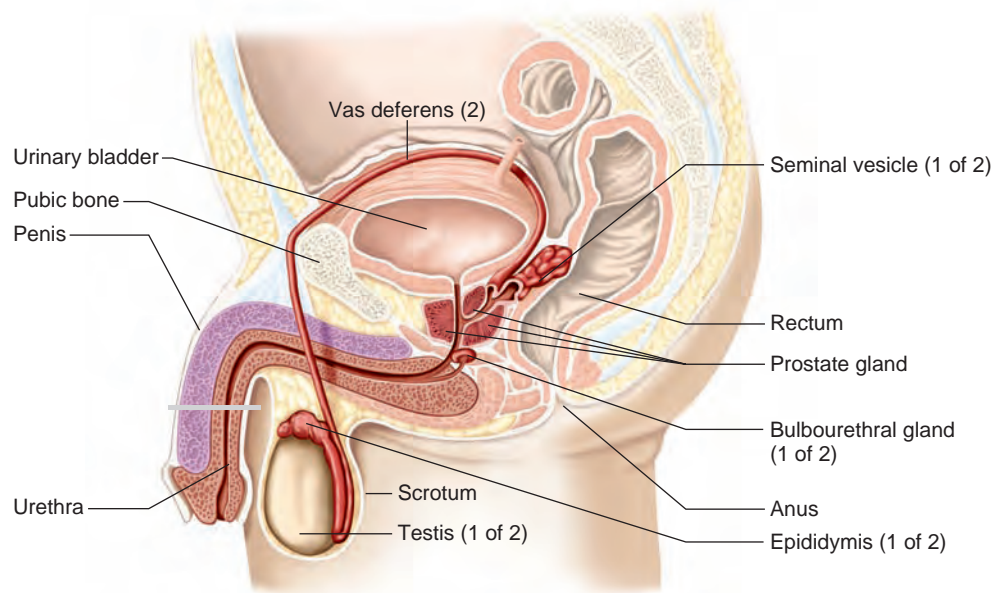
The formation of a new individual begins with a **sperm** from a male and an **oocyte** (also called an egg) from a female. Sperm and oocytes are **gametes**, or sex cells. They provide a mechanism for forming a new individual that mixes genetic material from past generations. Because there are so many genes and so many variants of them, each person (except for identical multiples) has a unique combination of inherited traits.

Sperm and oocytes are produced in the reproductive system. The reproductive organs are organized similarly in the male and female. Each system has

- paired structures, called **gonads**, where the sperm and oocytes are manufactured;
- tubules to transport these cells;
- hormones and secretions that control reproduction.

#### The Male

Sperm cells develop within a 125-meter-long network of seminiferous tubules, which are packed into paired, oval organs



**Figure 3.1 The human male reproductive system.** Sperm cells are manufactured within the seminiferous tubules, which wind tightly within the testes, which descend into the scrotum. The prostate gland, seminal vesicles, and bulbourethral glands add secretions to the sperm cells to form seminal fluid. Sperm mature and are stored in the epididymis and exit through the vas deferens. The paired vasa deferentia join in the urethra, which transports seminal fluid from the body.

called **testes** (sometimes called testicles) (**figure 3.1**). The testes are the male gonads. They lie outside the abdomen within a sac called the **scrotum**. This location keeps the testes cooler than the rest of the body, which is necessary for sperm to develop. Leading from each testis is a tightly coiled tube, the **epididymis**, in which sperm cells mature and are stored. Each epididymis continues into another tube, the **vas deferens**. Each vas deferens bends behind the bladder and joins the urethra, which is the tube that carries sperm and urine out through the penis.

Along the sperm's path, three glands add secretions. The vasa deferentia pass through the prostate gland, which produces a thin, milky, alkaline fluid that activates the sperm to swim. Opening into the vas deferens is a duct from the seminal vesicles, which secrete fructose (an energy-rich sugar) and hormonelike prostaglandins, which may stimulate contractions in the female that help sperm and oocyte meet. The bulbourethral glands, each about the

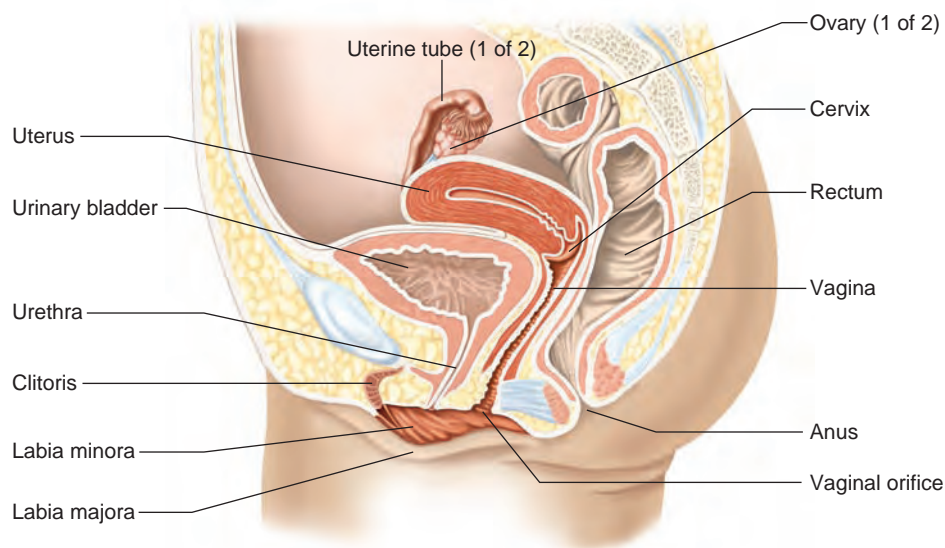
size of a pea, join the urethra where it passes through the body wall. They secrete an alkaline mucus that coats the urethra before sperm are released. All of these secretions combine to form the seminal fluid that carries sperm.

During sexual arousal, the penis becomes erect so that it can penetrate and deposit sperm in the female reproductive tract. At the peak of sexual stimulation, a pleasurable sensation called **orgasm** occurs, accompanied by rhythmic muscular contractions that eject the sperm from each vas deferens through the urethra and out the penis. The discharge of sperm from the penis, called **ejaculation**, delivers about 200 to 600 million sperm cells.

#### The Female

The female sex cells develop within paired organs in the abdomen called **ovaries** (**figure 3.2**), which are the female gonads. Within each ovary of a newborn girl are about a million immature oocytes. Each





**Figure 3.2 The human female reproductive system.** Oocytes mature in the paired ovaries. Once a month after puberty, an ovary releases one oocyte, which is drawn into a nearby uterine tube. If a sperm fertilizes the oocyte in the uterine tube, the fertilized ovum continues into the uterus, where for nine months it divides and develops. If the oocyte is not fertilized, the body expels it, along with the built-up uterine lining. This is the menstrual flow.

individual oocyte nestles within nourishing follicle cells, and each ovary houses oocytes in different stages of development. After puberty, about once a month, one ovary releases the most mature oocyte. Beating cilia sweep the mature oocyte into the fingerlike projections of one of two uterine (also called fallopian) tubes. The tube carries the oocyte into a muscular, saclike organ called the uterus, or womb.

The released oocyte may encounter a sperm. This usually occurs in a uterine tube. If the sperm enters the oocyte and the DNA of the two gametes merges into a new nucleus, the result is a fertilized ovum. After about a day, this first cell rapidly divides while moving through the uterine tube. It then settles into the lining of the uterus, where it may continue to divide and an embryo develop. If fertilization does not occur, the oocyte, along with much of the uterine lining, is shed as the menstrual flow. Hormones coordinate the monthly menstrual cycle.

The lower end of the uterus narrows and leads to the cervix, which opens into the tubelike vagina. The vaginal opening is protected on the outside by two pairs of fleshy

folds. At the upper juncture of both pairs is a 2-centimeter-long structure called the clitoris, which is anatomically similar to the penis. Rubbing the clitoris triggers female orgasm. Hormones control the cycle of oocyte maturation and the preparation of the uterus to nurture a fertilized ovum.

## Key Concepts

1. Sperm develop in the seminiferous tubules, mature and collect in each epididymis, enter the vasa deferentia, and move through the urethra in the penis. The prostate gland adds an alkaline fluid, seminal vesicles add fructose and prostaglandins, and bulbourethral glands secrete mucus to form seminal fluid.
2. In the female, ovaries contain oocytes. Each month, an ovary releases an oocyte, which enters a uterine tube leading to the uterus. If the oocyte is fertilized, it begins rapid cell division and nestles into the uterine lining to divide and develop. Otherwise, the oocyte exits the body. Hormones control the cycle of oocyte development.

## 3.2 Meiosis

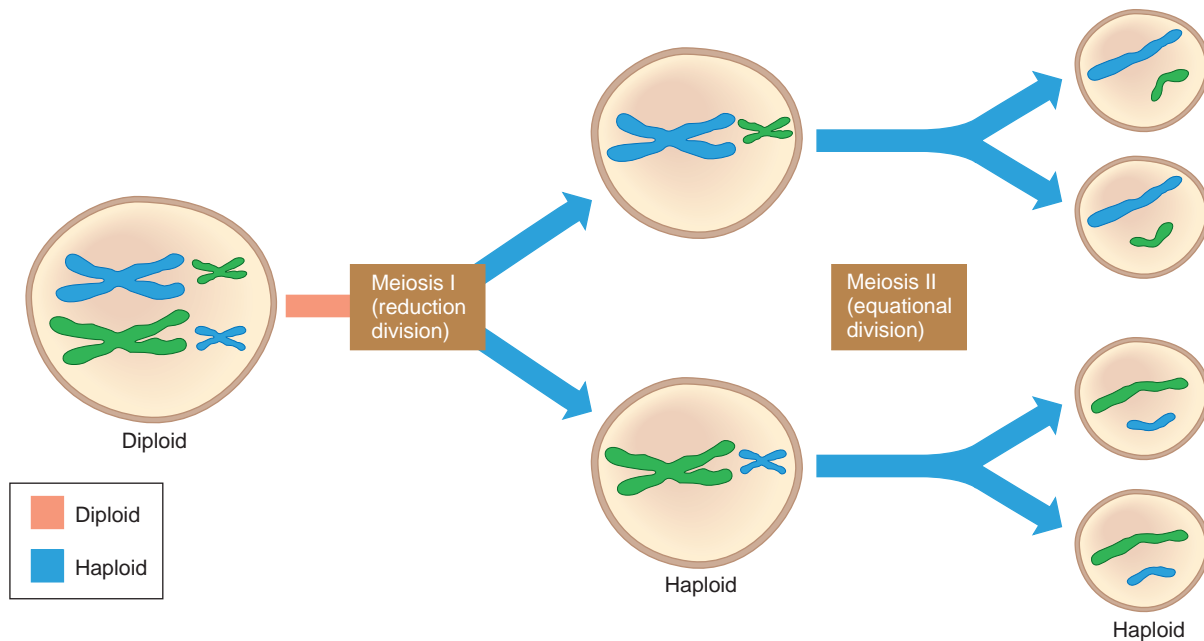
Gametes form from special cells, called germline cells, in a type of cell division called **meiosis** that halves the chromosome number. A further process, maturation, sculpts the distinctive characteristics of sperm and oocyte. The organelle-packed oocyte has 90,000 times the volume of the streamlined sperm, which is little more than a genetic package atop a propulsion system.

Unlike other cells in the human body, gametes contain 23 different chromosomes—half the usual amount of genetic material, but still a complete genome. Somatic (non-sex) cells contain 23 pairs, or 46 chromosomes. One member of each pair comes from the person's mother and one comes from the father. The chromosome pairs are called **homologous pairs**, or *homologs* for short. Homologs have the same genes in the same order but may carry different alleles, or forms, of the same gene. Gametes are **haploid** ( $1n$ ), which means that they have only one of each type of chromosome and therefore one copy of the human genome. Somatic cells are **diploid** ( $2n$ ), signifying that they have two copies of the genome.

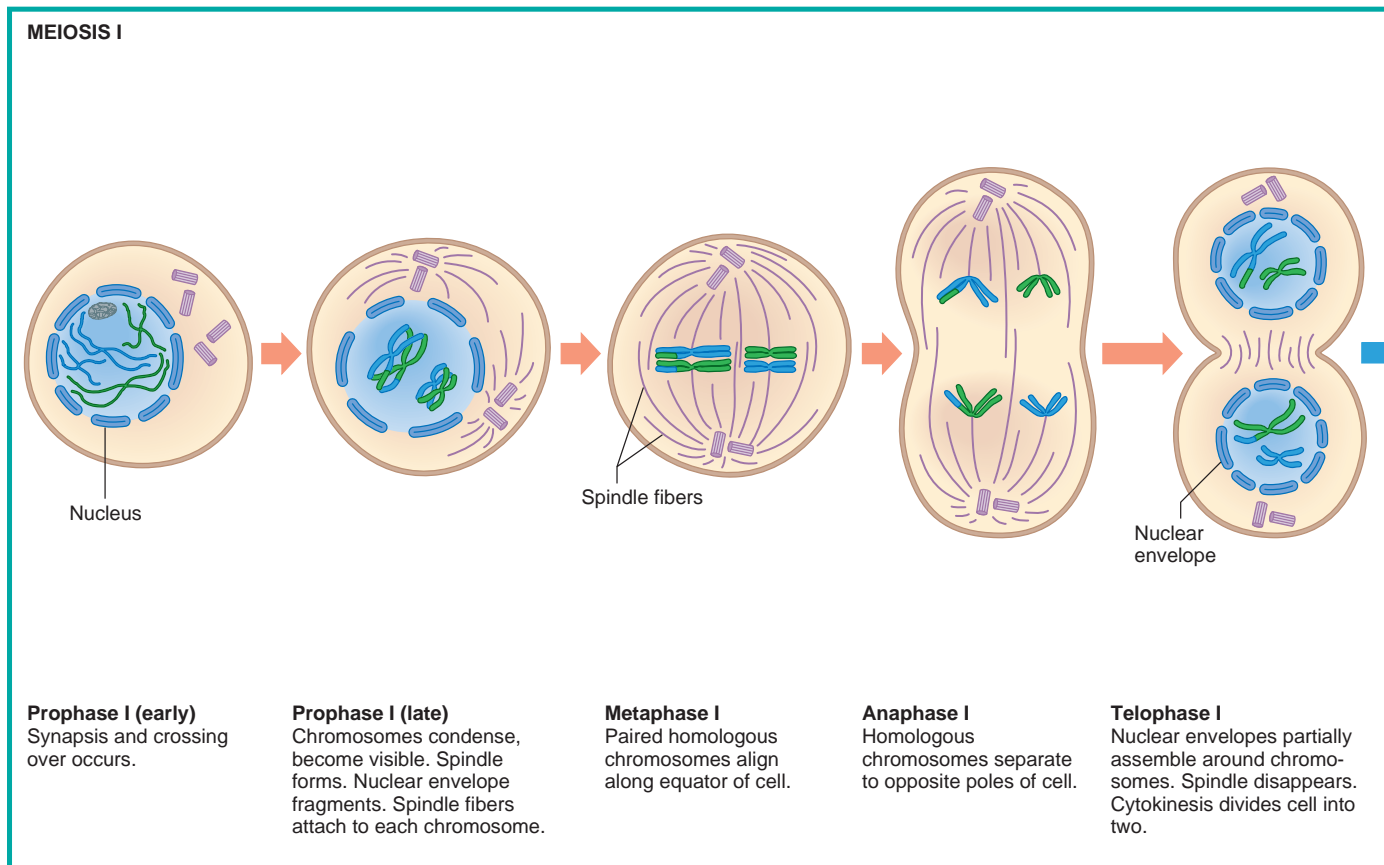
Halving the number of chromosomes during gamete formation makes sense. If the sperm and oocyte each contained 46 chromosomes, the fertilized ovum would contain twice the normal number of chromosomes, or 92. Such a genetically overloaded cell, called a polyploid, usually does not develop. About one in a million newborns is polyploid, and has abnormalities in all organ systems and usually only lives a few days. However, studies on spontaneously aborted embryos indicate that about 1 percent of conceptions have three chromosome sets instead of the normal two. Therefore, most polyploid embryos do not survive to be born.

In addition to producing gametes, meiosis mixes up trait combinations. For example, a person might produce one gamete containing alleles encoding green eyes and freckles, yet another gamete with alleles encoding brown eyes and no freckles. Meiosis explains why siblings differ genetically from each other and from their parents.

In a much broader sense, meiosis, as the mechanism of sexual reproduction, provides genetic diversity, which enables a population to survive a challenging environmental change. A population of sexually reproducing



**Figure 3.3 Overview of meiosis.** Meiosis is a form of cell division in which certain cells are set aside and give rise to haploid gametes. This simplified illustration follows the fate of two chromosome pairs. In actuality, the first meiotic division reduces the number of chromosomes to 23, all in the replicated form. In the second meiotic division, the cells essentially undergo mitosis. The result of the two meiotic divisions (in this illustration and in reality) is four haploid cells. In this illustration, homologous pairs of chromosomes are indicated by size, and parental origin of chromosomes by color.



**Figure 3.4 Meiosis.** An actual human cell undergoing meiosis has 23 chromosome pairs.

organisms is made up of individuals with different genotypes and phenotypes. In contrast, a population of asexually reproducing organisms consists of identical individuals. Should a new threat arise, such as an infectious disease that kills only individuals with a certain genotype, then the entire asexual population could be wiped out. However, in a sexually reproducing population, individuals that inherited a certain combination of genes might survive. This differential survival of certain genotypes is the basis of evolution, discussed in chapter 16.

Meiosis entails two divisions of the genetic material. The first division is called **reduction division** (or meiosis I) because it reduces the number of replicated chromosomes from 46 to 23. The second division, called the **equational division** (or meiosis II), produces four cells from the two cells formed in the first division by splitting the replicated chromosomes. **Figure 3.3** shows an overview of the process, and **figure 3.4** depicts the major events of each stage.

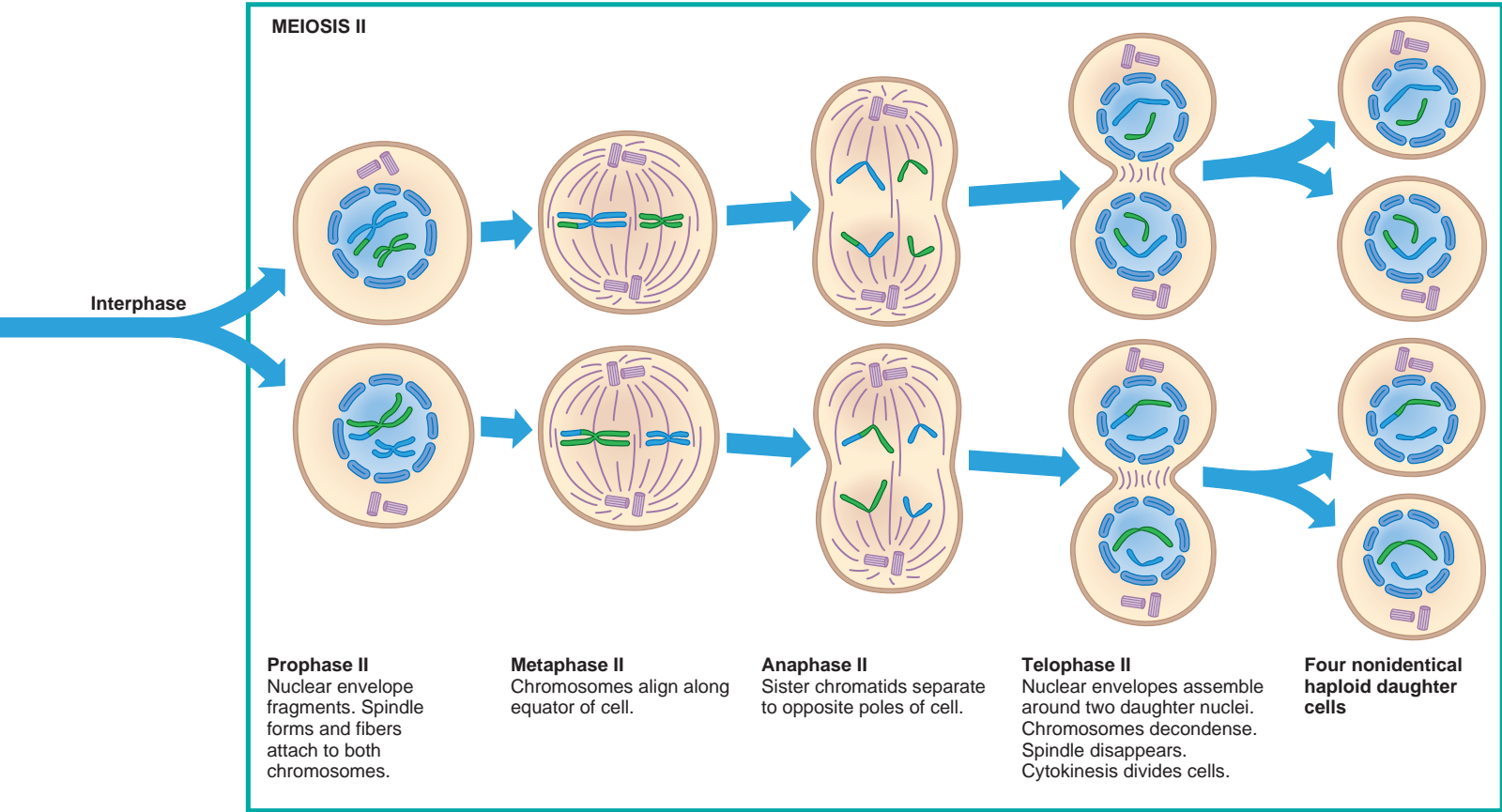
**Table 3.1**  
Comparison of Mitosis and Meiosis

Mitosis	Meiosis
One division	Two divisions
Two daughter cells per cycle	Four daughter cells per cycle
Daughter cells genetically identical	Daughter cells genetically different
Chromosome number of daughter cells same as that of parent cell ( $2n$ )	Chromosome number of daughter cells half that of parent cell ( $1n$ )
Occurs in somatic cells	Occurs in germline cells
Occurs throughout life cycle	In humans, completes after sexual maturity
Used for growth, repair, and asexual reproduction	Used for sexual reproduction, producing new gene combinations

As in mitosis, meiosis occurs after an interphase period when DNA is replicated (doubled) (**table 3.1**). For each chromosome pair in the cell undergoing meiosis, one homolog comes from the person’s mother, and one from the father. In figures 3.3

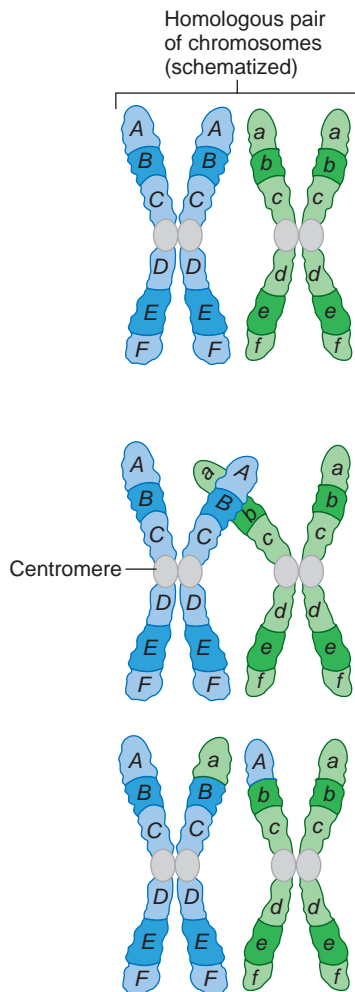
and 3.4, the colors represent the contributions of the two parents, whereas size indicates different chromosomes.

After interphase, prophase I (so called because it is the prophase of meiosis I) begins as the replicated chromosomes condense





and become visible when stained. A spindle forms. Toward the middle of prophase I, the homologs line up next to one another, gene by gene, in an event called **synapsis**. A mixture of RNA and protein holds the chromosome pairs together. At this time, the homologs exchange parts in a process called **crossing over** (**figure 3.5**). All four chromatids that comprise each homologous chromosome pair are pressed together as exchanges occur. After crossing over, each homolog bears genes from both parents. (Prior to this, all of the genes on a homolog were derived from one parent.) New gene combinations arise from crossing over when the parents carry different alleles.



**Figure 3.5 Crossing over recombines genes.** Crossing over helps to generate genetic diversity by recombining genes and thereby mixing parental traits. The capital and lowercase forms of the same letter represent different variants (alleles) of the same gene.

Toward the end of prophase I, the synapsed chromosomes separate but remain attached at a few points along their lengths.

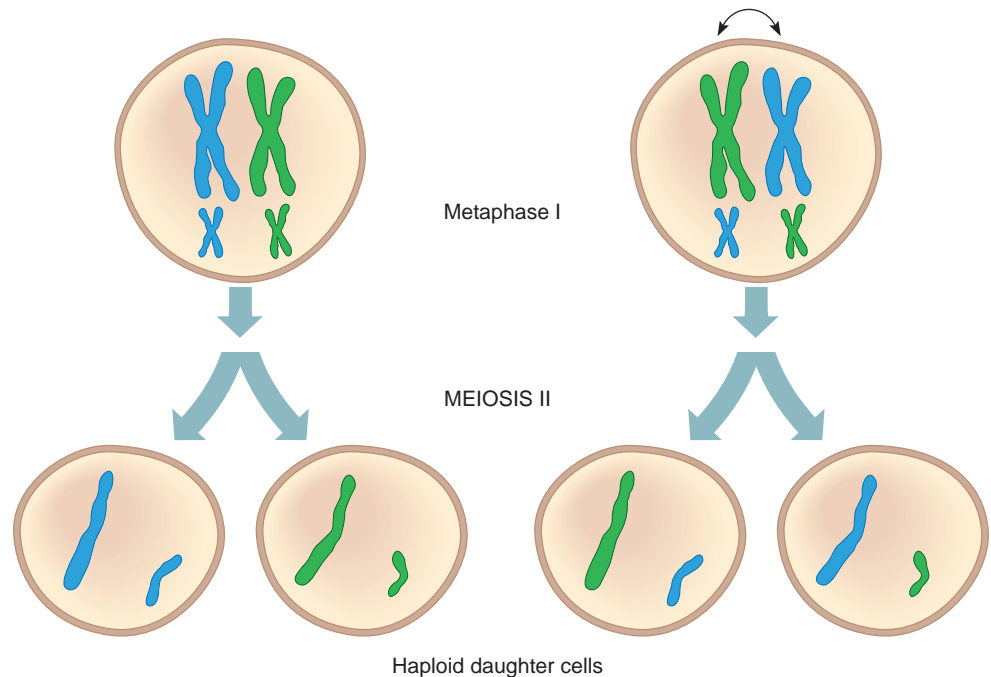
To understand how crossing over mixes trait combinations, consider a simplified example. Suppose that homologs carry genes for hair color, eye color, and finger length. One of the chromosomes carries alleles for blond hair, blue eyes, and short fingers. Its homolog carries alleles for black hair, brown eyes, and long fingers. After crossing over, one of the chromosomes might bear alleles for blond hair, brown eyes, and long fingers, and the other might bear alleles for black hair, blue eyes, and short fingers.

Meiosis continues in metaphase I, when the homologs align down the center of the cell. Each member of a homolog pair attaches to a spindle fiber at opposite poles. The pattern in which the chromosomes align during metaphase I is important in generating genetic diversity. For each homolog pair, the pole the maternally or paternally derived member goes to is random. It is a little like

the number of different ways that 23 boys and 23 girls can line up in boy-girl pairs.

The greater the number of chromosomes, the greater the genetic diversity generated at this stage. For two pairs of homologs, four ( $2^2$ ) different metaphase alignments are possible. For three pairs of homologs, eight ( $2^3$ ) different alignments can occur. Our 23 chromosome pairs can line up in 8,388,608 ( $2^{23}$ ) different ways. This random alignment of chromosomes causes **independent assortment** of the genes that they carry. Independent assortment means that the fate of a gene on one chromosome is not influenced by a gene on a different chromosome (**figure 3.6**). Independent assortment accounts for a basic law of inheritance discussed in chapter 4.

Homologs separate in anaphase I and finish moving to opposite poles by telophase I. This establishes a haploid set of still-replicated chromosomes at each end of the stretched-out cell. Unlike in mitosis, the centromeres of each homolog in meiosis I remain together. During a second



**Figure 3.6 Independent assortment.** The pattern in which homologs randomly align during metaphase I determines the combination of maternally and paternally derived chromosomes in the daughter cells. Two pairs of chromosomes can align in two different ways to produce four different possibilities in the daughter cells. The potential variability that meiosis generates skyrockets when one considers all 23 chromosome pairs and the effects of crossing over.

interphase, chromosomes unfold into very thin threads. Proteins are manufactured, but DNA is not replicated a second time. The single DNA replication, followed by the double division of meiosis, halves the chromosome number.

Prophase II marks the start of the second meiotic division. The chromosomes are again condensed and visible. In metaphase II, the replicated chromosomes align down the center of the cell. In anaphase II, the centromeres part, and the newly formed chromosomes, each now in the unreplicated form, move to opposite poles. In telophase II, nuclear envelopes form around the four nuclei, which then separate into individual cells. The net result of meiosis is four haploid cells, each carrying a new assortment of genes and chromosomes that represent a single copy of the genome.

Meiosis generates astounding genetic variety. Any one of a person's more than 8 million possible combinations of chromosomes can meet with any one of the more than 8 million combinations of a partner, raising potential variability to more than 70 trillion ( $8,388,608^2$ ) genetically unique individuals! Crossing over contributes even more genetic variability.

## Key Concepts

1. The haploid sperm and oocyte are derived from diploid germline cells by meiosis and maturation.
2. Meiosis maintains the chromosome number over generations and mixes gene combinations.
3. In the first meiotic (or reduction) division, the number of replicated chromosomes is halved.
4. In the second meiotic (or equational) division, each of two cells from the first division divides again, yielding four cells from the original one.
5. Chromosome number is halved because the DNA replicates once, but the cell divides twice.
6. Crossing over and independent assortment generate further genotypic diversity by creating new combinations of alleles.

cell components create their distinctions. The cells of the maturing male and female proceed through similar stages, but with sex-specific terminology and different time-tables. A male begins manufacturing sperm at puberty and continues throughout life, whereas a female begins meiosis when she is a fetus. Meiosis in the female completes only if a sperm fertilizes an oocyte.

## Sperm Formation

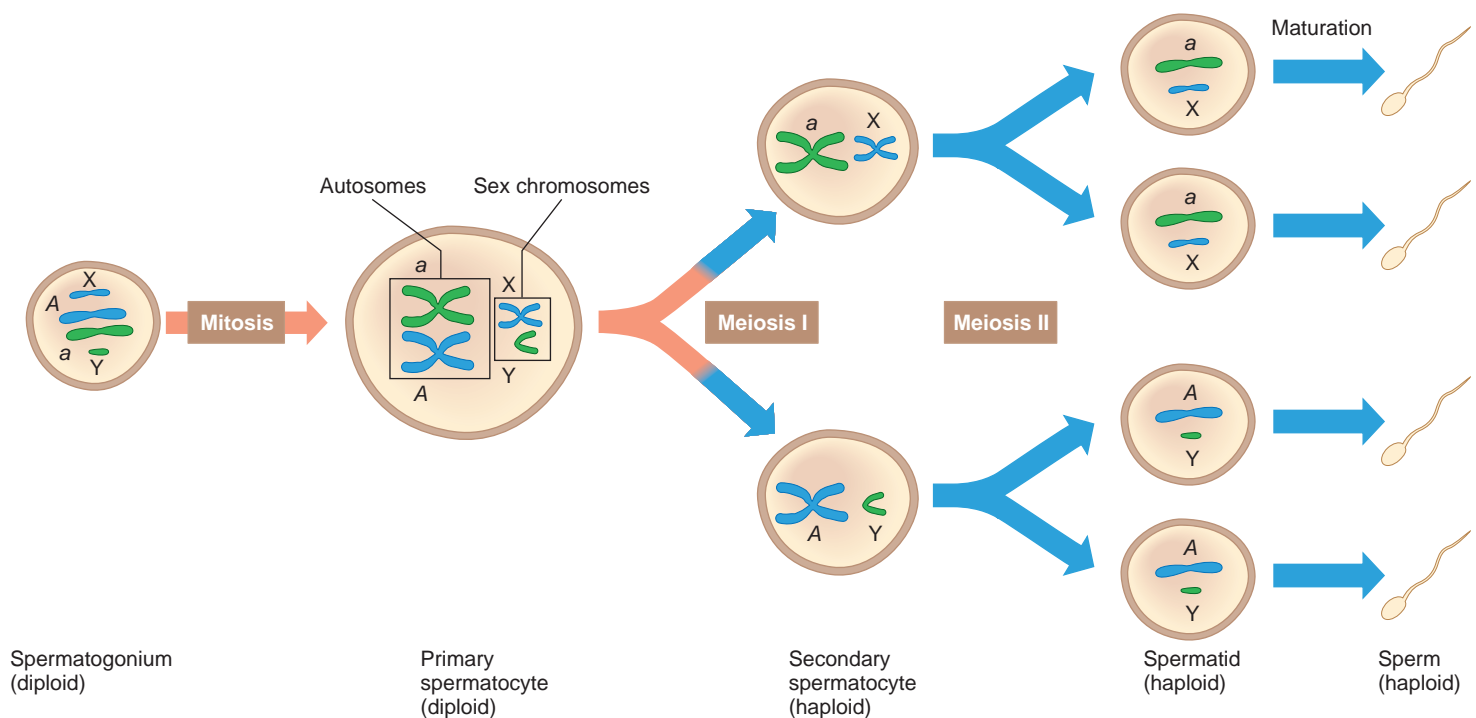
**Spermatogenesis**, the formation of sperm cells, begins in a diploid stem cell called a **spermatogonium** (figure 3.7). This cell divides mitotically, yielding two daughter cells. One continues to specialize into a mature sperm, and the other remains a stem cell.

Bridges of cytoplasm join several spermatogonia, and their daughter cells enter meiosis together. As they mature, these spermatogonia accumulate cytoplasm and replicate their DNA, becoming primary spermatocytes.

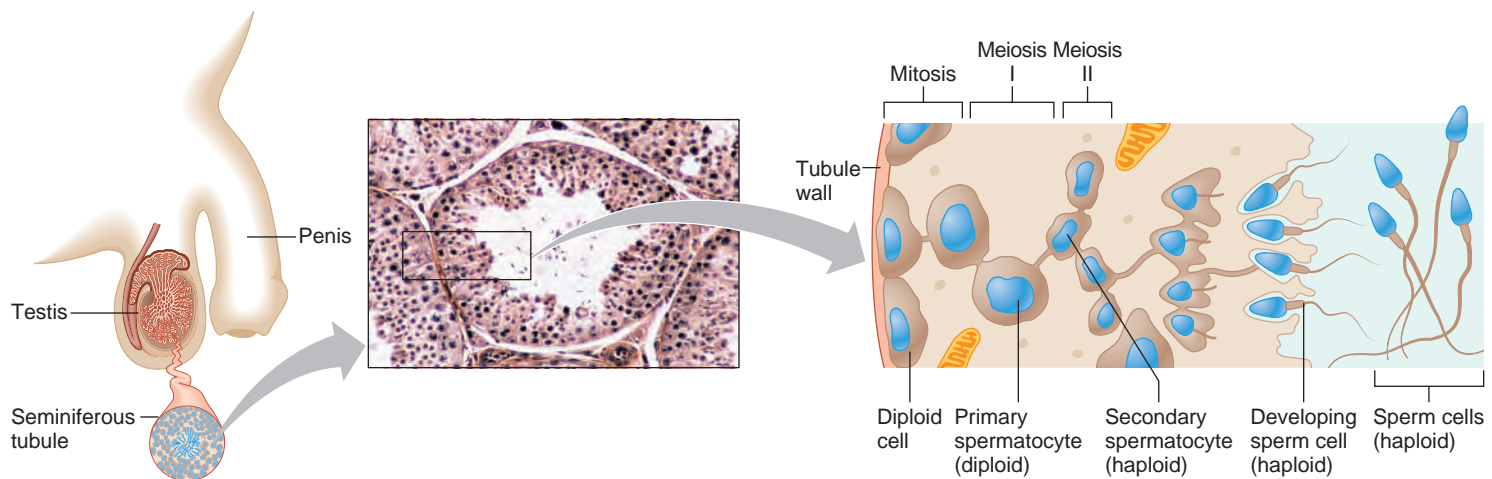
During reduction division (meiosis I), each primary spermatocyte divides, forming two equal-sized haploid cells called secondary spermatocytes. In meiosis II, each

## 3.3 Gamete Maturation

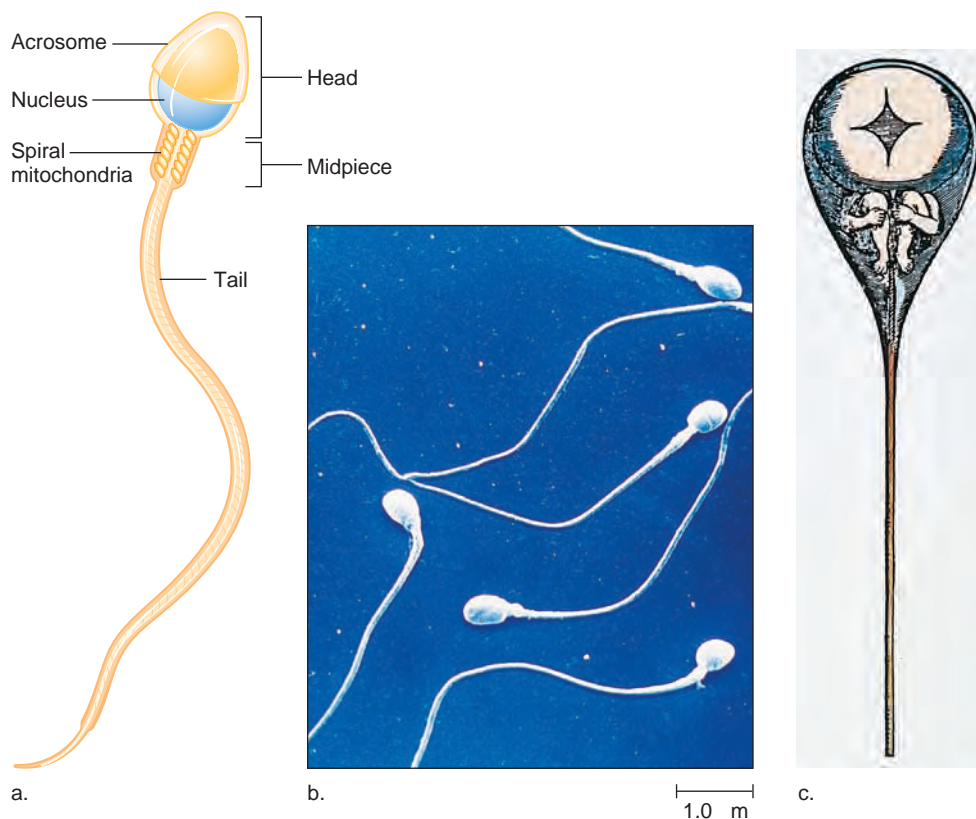
Meiosis occurs in both sexes, but further steps elaborate the very different-looking sperm and oocyte. Each type of gamete is haploid, but different distributions of other



**Figure 3.7 Sperm formation (spermatogenesis).** Primary spermatocytes have the normal diploid number of 23 chromosome pairs. The large pair of chromosomes represents autosomes (non-sex chromosomes). The X and Y chromosomes are sex chromosomes.



**Figure 3.8 Meiosis produces sperm cells.** Diploid cells divide through mitosis in the linings of the seminiferous tubules. Some of the daughter cells then undergo meiosis, producing haploid spermatocytes, which differentiate into mature sperm cells.



**Figure 3.9 Sperm.** (a) A sperm has distinct regions that assist in delivering DNA to an oocyte. (b) Scanning electron micrograph of human sperm cells. (c) This 1694 illustration by Dutch histologist Niklass Hartsoeker presents a once-popular hypothesis that a sperm carries a preformed human called a homunculus.

secondary spermatocyte divides to yield two equal-sized spermatids. Each spermatid then develops the characteristic sperm tail, or flagellum. The base of the tail has many mitochondria, which will split ATP molecules to release energy that will propel the sperm inside the female reproductive tract. After spermatid differentiation,

some of the cytoplasm connecting the cells falls away, leaving mature, tadpole-shaped spermatozoa (singular *spermatozoon*), or sperm. **Figure 3.8** presents an anatomical view showing the stages of spermatogenesis within the seminiferous tubules.

A sperm, which is a mere 0.006 centimeter (0.0023 inch) long, must travel about

18 centimeters (7 inches) to reach an oocyte. Each sperm cell consists of a tail, body or midpiece, and a head region (**figure 3.9**). A membrane-covered area on the front end, the acrosome, contains enzymes that help the cell penetrate the protective layers around the oocyte. Within the large sperm head, DNA is wrapped around proteins. The sperm's DNA at this time is genetically inactive. A male manufactures trillions of sperm in his lifetime. Although many of these will come close to an oocyte, very few will actually touch one.

Meiosis in the male has built-in protections that help prevent sperm from causing birth defects. Spermatogonia that are exposed to toxins tend to be so damaged that they never mature into sperm. More mature sperm cells exposed to toxins are often so damaged that they cannot swim.

## Key Concepts

1. Spermatogonia divide mitotically, yielding one stem cell and one cell that accumulates cytoplasm and becomes a primary spermatocyte.
2. In meiosis I, each primary spermatocyte halves its genetic material to form two secondary spermatocytes.
3. In meiosis II, each secondary spermatocyte divides, yielding two equal-sized spermatids attached by bridges of cytoplasm. Maturing spermatids separate and shed some cytoplasm.
4. A mature sperm has a tail, body, and head, with an enzyme-containing acrosome covering the head.



## Oocyte Formation

Meiosis in the female, called **oogenesis** (egg making), begins with a diploid cell, an **oogonium**. Unlike male cells, oogonia are not attached. Instead, follicle cells surround each oogonium. As each oogonium grows, cytoplasm accumulates, DNA replicates, and the cell becomes a primary oocyte. The ensuing

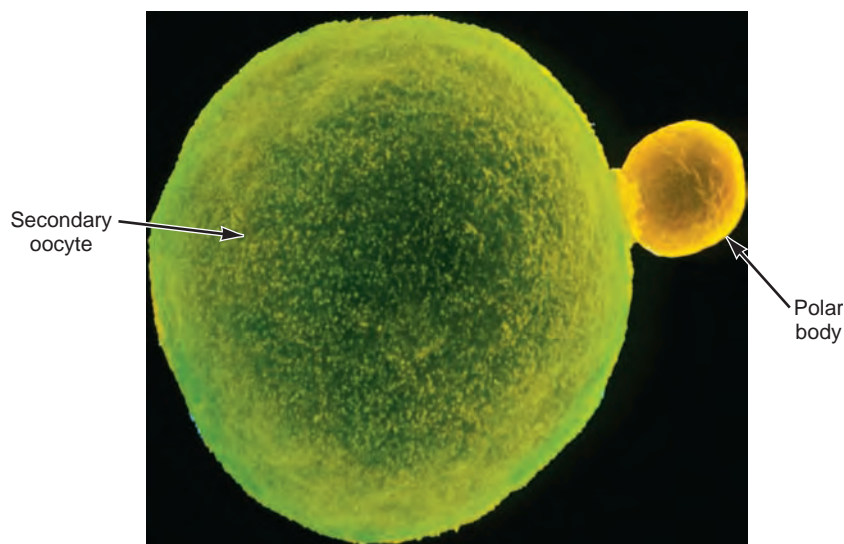
meiotic division in oogenesis, unlike the male pathway, produces cells of different sizes.

In meiosis I, the primary oocyte divides into two cells: a small cell with very little cytoplasm, called a first **polar body**, and a much larger cell called a secondary oocyte (**figure 3.10**). Each cell is haploid, with the chromosomes in replicated form. In meiosis II, the tiny first polar body may

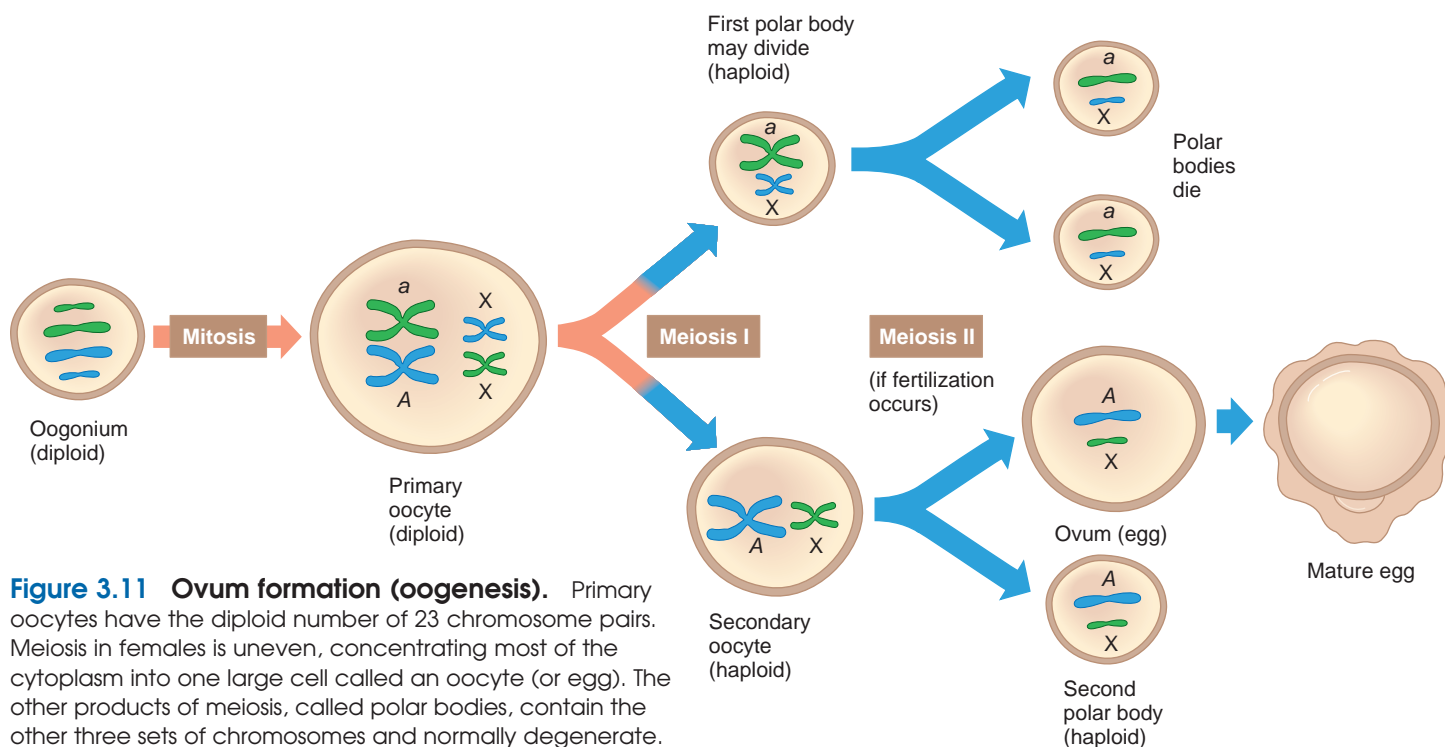
divide to yield two polar bodies of equal size, with unreplicated chromosomes; or the first polar body may decompose. The secondary oocyte, however, divides unequally in meiosis II to produce another small polar body, with unreplicated chromosomes, and the mature egg cell, or ovum, which contains a large volume of cytoplasm. **Figure 3.11** summarizes meiosis in the female, and **figure 3.12** provides an anatomical view of the process.

Most of the cytoplasm among the four meiotic products in the female ends up in only one cell, the ovum. The woman's body absorbs the polar bodies, which normally play no further role in development. Rarely, a sperm fertilizes a polar body. When this happens, the woman's hormones respond as if she is pregnant, but a disorganized clump of cells that is not an embryo grows for a few weeks, and then leaves the woman's body. This event is a type of miscarriage called a "blighted ovum."

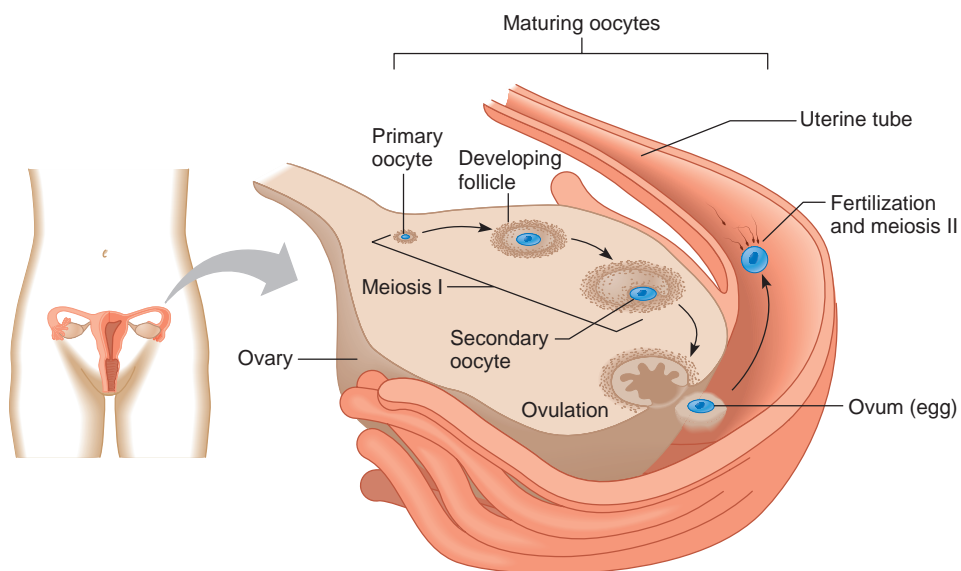
Before birth, a female's million or so oocytes arrest in prophase I. (This means that when your grandmother was pregnant with your mother, the oocyte that would be fertilized and eventually become you was already there.) By puberty, about 400,000 oocytes remain. After puberty, meiosis I continues in one or several oocytes each month, but halts again at metaphase II. In response to specific hormonal cues each month, one ovary releases a secondary oocyte; this event is ovulation. The oocyte drops into a uterine



**Figure 3.10** Meiosis in a female produces a secondary oocyte and a polar body. Unequal division enables the cell destined to become a fertilized ovum to accumulate most of the cytoplasm and organelles from the primary oocyte, but with only one genome's worth of DNA. The oocyte accumulates abundant cytoplasm that would have gone into the meiotic product that became the polar body if the division had been equal.



**Figure 3.11** Ovum formation (oogenesis). Primary oocytes have the diploid number of 23 chromosome pairs. Meiosis in females is uneven, concentrating most of the cytoplasm into one large cell called an oocyte (or egg). The other products of meiosis, called polar bodies, contain the other three sets of chromosomes and normally degenerate.



**Figure 3.12 The making of oocytes.** Oocytes develop within the ovary in protective follicles. An ovary contains many oocytes in various stages of maturation. After puberty, the most mature oocyte in one ovary bursts out each month, an event called ovulation.

tube, where waving cilia move it toward the uterus. Along the way, if a sperm penetrates the oocyte membrane, then female meiosis completes, and a fertilized ovum forms. If the secondary oocyte is not fertilized, it degenerates and leaves the body in the menstrual flow, meiosis never completed.

A female ovulates about 400 oocytes between puberty and menopause. (However, experiments in mice suggest that stem cells may produce oocytes even past menopause.) Most oocytes are destined to degrade, because fertilization is very rare. Only one in three of the oocytes that do meet and merge with a sperm cell will continue to grow, divide, and specialize to eventually form a new individual.

## Key Concepts

1. An oogonium accumulates cytoplasm and replicates its DNA, becoming a primary oocyte.
2. In meiosis I, the primary oocyte divides, forming a small polar body and a large, haploid secondary oocyte.
3. In meiosis II, the secondary oocyte divides, yielding another small polar body and a mature haploid ovum.
4. Oocytes arrest at prophase I until puberty, after which one or several oocytes complete the first meiotic division each month. The second meiotic division completes at fertilization.

## 3.4 Prenatal Development

A prenatal human is considered an **embryo** for the first eight weeks. During this time, rudiments of all body parts form. The embryo in the first week is considered to be in a “preimplantation” stage because it has not yet settled into the uterine lining. Some biologists do not consider a prenatal human an embryo until it has tissue layers, at about 2 weeks.

Prenatal development after the eighth week is the fetal period. This is the time when structures grow and specialize. From the start of the ninth week until birth, the prenatal human organism is a **fetus**.

## Fertilization

Hundreds of millions of sperm cells are deposited in the vagina during sexual intercourse. A sperm cell can survive in the woman’s body for up to three days, but the oocyte can only be fertilized in the 12 to 24 hours after ovulation.

The woman’s body helps sperm reach an oocyte. A process in the female called capacitation chemically activates sperm, and the oocyte secretes a chemical that attracts sperm. Sperm are also assisted by contractions of the female’s muscles and by their moving tails. Still, only 200 or so sperm come near the oocyte.

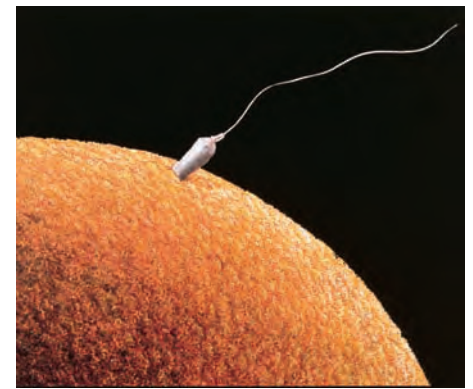
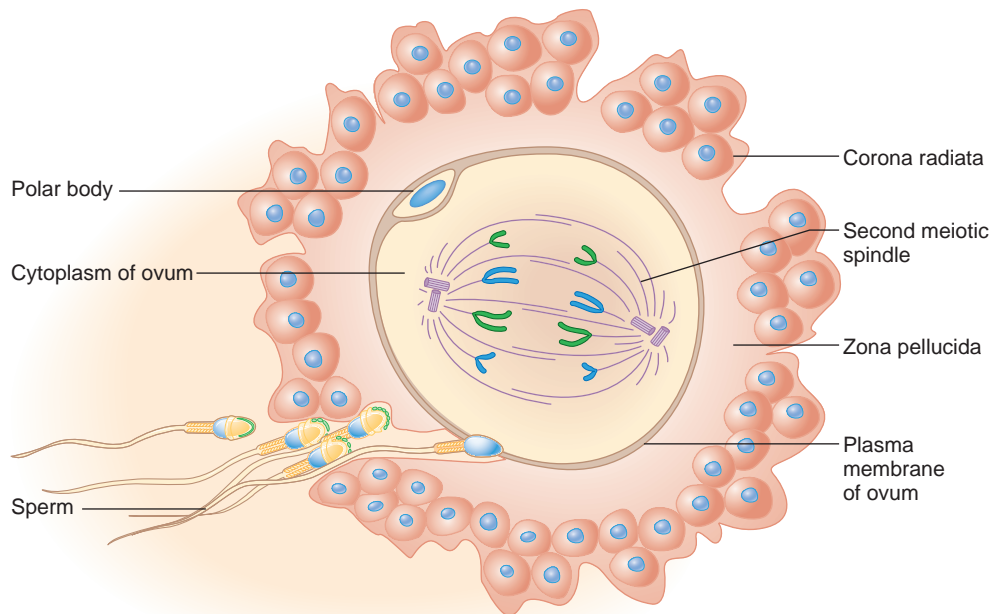
A sperm first contacts a covering of follicle cells, called the corona radiata, that guards a secondary oocyte. The sperm’s acrosome then bursts, releasing enzymes that bore through a protective layer of glycoprotein (the zona pellucida) beneath the corona radiata. Fertilization, or conception, begins when the outer membranes of the sperm and secondary oocyte meet (**figure 3.13**). The encounter is dramatic. A wave of electricity spreads physical and chemical changes across the entire oocyte surface—changes that keep other sperm out. More than one sperm can enter an oocyte, but the resulting cell has too much genetic material for development to follow.

Usually only the sperm’s head enters the oocyte. Within 12 hours of the sperm’s penetration, the ovum’s nuclear membrane disappears, and the two sets of chromosomes, called pronuclei, approach one another. Within each pronucleus, DNA replicates. Fertilization completes when the two genetic packages meet and merge, forming the genetic instructions for a new individual. The fertilized ovum is called a **zygote**. The Bioethics: Choices for the Future reading describes cloning, which is a way to start development without a fertilized egg.

## Cleavage and Implantation

About a day after fertilization, the zygote divides by mitosis, beginning a period of frequent cell division called **cleavage** (**figure 3.14**). The resulting early cells are called **blastomeres**. When the blastomeres form a solid ball of sixteen or more cells, the embryo is called a **morula** (Latin for “mulberry,” which it resembles).

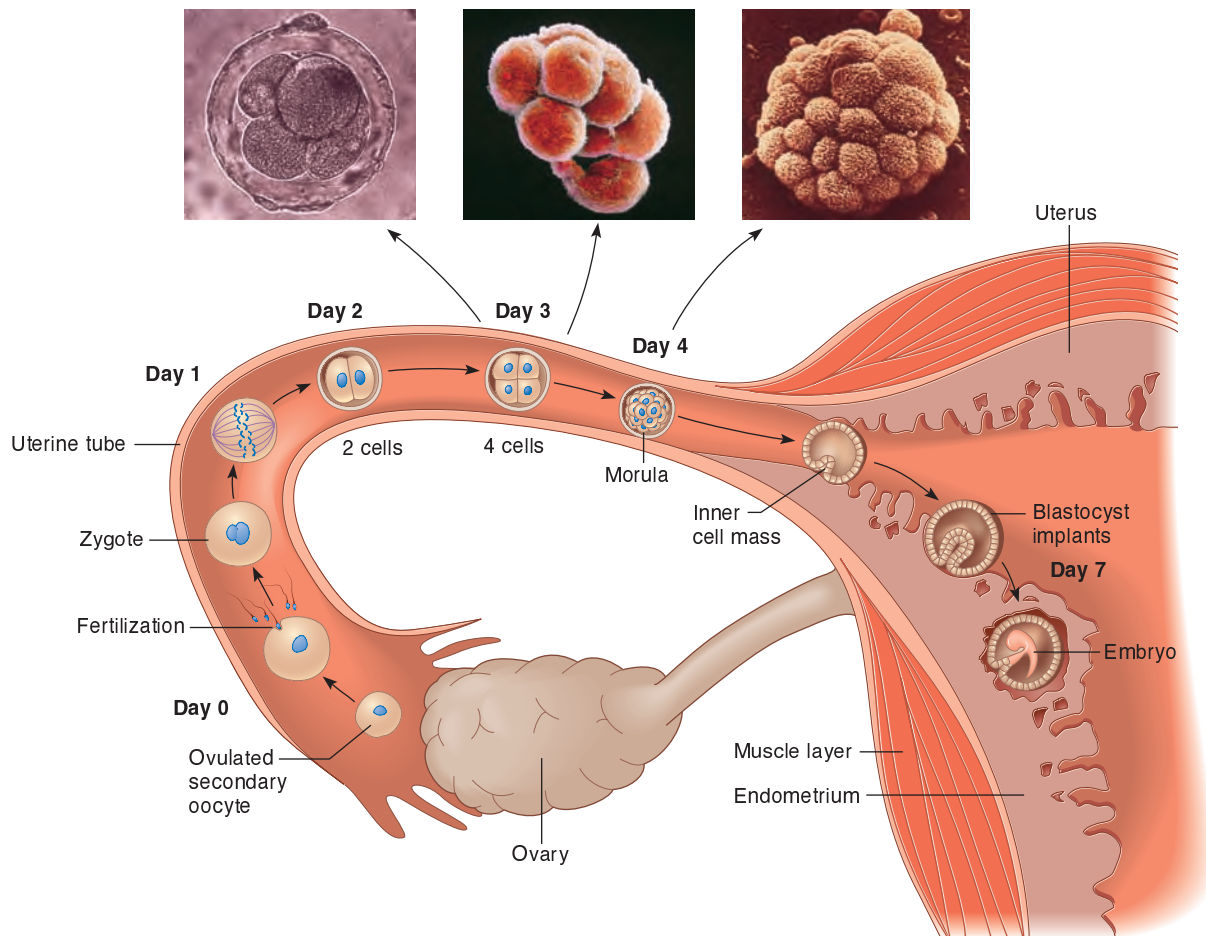
During cleavage, organelles and molecules from the secondary oocyte’s cytoplasm still control cellular activities, but some of the embryo’s genes begin to function. The ball of cells hollows out, and its center fills with fluid, creating a **blastocyst**—the “cyst” refers to the fluid-filled center. Some of the cells form a clump on the inside lining called the **inner cell mass**. (see figure 2.23). Formation of the inner cell mass is the first event that distinguishes cells from each other in terms of their



b.

### Figure 3.13 Fertilization.

(a) Fertilization by a sperm cell induces the oocyte (arrested in metaphase II) to complete meiosis. Before fertilization occurs, the sperm's acrosome bursts, spilling enzymes that help the sperm's nucleus enter the oocyte. (b) A series of chemical reactions ensues that helps to ensure that only one sperm nucleus enters an oocyte.



**Figure 3.14 Cleavage: From ovulation to implantation.** The zygote forms in the uterine tube when a sperm nucleus fuses with the nucleus of an oocyte. The first divisions proceed while the zygote moves toward the uterus. By day 7, the zygote, now called a blastocyst, begins to implant in the uterine lining.



## Why a Clone Is Not an Exact Duplicate

Cloning is the creation of a genetic replica of an individual. This is in contrast to normal reproduction and development, in which genetic material from two individuals combines. In fiction, renegade scientists have cloned Nazis, politicians, dinosaurs, and organ donors for wealthy people, willing and not. Real scientists have cloned sheep, mice, cats, pigs, and amphibians.

Cloning transfers a nucleus from a somatic cell into an oocyte whose nucleus has been removed, and then develops new cells or a new individual from the original manipulated cell. The technique is more accurately called “somatic cell nuclear transfer” (SCNT) or just “nuclear transfer.” These are more descriptive and precise terms than “cloning” and have fewer negative connotations. Figure 2.24 illustrates SCNT to supply stem cells tailored to a sick or injured individual. In contrast to SCNT, so-called reproductive cloning seeks to create a baby using the nucleus from the cell of an individual who will then, supposedly, be duplicated. But the premises behind reproductive cloning are flawed, for a clone is not an exact replica of an individual. Many of the distinctions between an individual and a clone arise from epigenetic

phenomena—effects that do not change genes, but alter their expression. There are other distinctions, too (parentheses indicate chapters that discuss these subjects further):

- **Premature cellular aging.** In some species, telomeres of chromosomes in the donor nucleus are shorter than those in the recipient cell (chapter 2). Premature aging, as evidenced in shortened telomeres, may be why the first cloned mammal, Dolly, died early of a severe respiratory infection.
- **Altered gene expression.** In normal development, for some genes, one copy is turned off, depending upon which parent transmits it. That is, some genes must be inherited from either the father or the mother to be active. This phenomenon is called genomic imprinting. In cloning, genes in a donor nucleus skip passing through a parent’s sperm or oocyte, and thus they are not imprinted. Lack of imprinting may cause cloned animals to be unusually large. Experiments in nonhuman cloned animals indicate that regulation of gene expression is abnormal at many times during prenatal development (chapter 5).
- **More mutations.** DNA from a donor cell has had years to accumulate mutations. Such a somatic mutation might not be noticeable in one of millions of somatic cells, but it could be devastating if that somatic cell nucleus is used to program the development of a new individual (chapter 11).
- **X inactivation.** At a certain time in early prenatal development in all female mammals, one X chromosome is inactivated. Whether that X chromosome is from the mother or the father occurs at random in each cell, creating an overall mosaic pattern of expression for genes on the X chromosome. The pattern of X inactivation of a female clone would most likely not match that of her nucleus donor, because X inactivation occurs in the embryo, not the first cell. (chapter 6).
- **Mitochondrial DNA.** Mitochondria contain DNA. A clone’s mitochondria descend from the recipient oocyte, not from the donor cell, because they are in the cytoplasm, not the nucleus.

relative positions, other than the inside and outside of the morula. The cells of the inner cell mass will continue developing to form the embryo. (Cells that can be used to generate embryonic stem cells come from the 8-celled cleavage embryo or the inner cell mass of a 5-day blastocyst, shown in Figure 2.23.)

A week after conception, the blastocyst begins to nestle into the woman’s uterine lining (endometrium). This event, called implantation, takes about a week. As it starts, the outermost cells of the embryo, called the trophoblast, secrete the “pregnancy hormone,” human chorionic gonadotropin (hCG), which prevents menstruation. hCG detected in a woman’s urine or blood is one sign of pregnancy.

### Key Concepts

1. Following sexual intercourse, sperm are capacitated and drawn to the secondary oocyte.
2. Acrosomal enzymes assist the sperm’s penetration of the oocyte. Chemical and electrical changes in the oocyte’s surface block additional sperm.
3. The two sets of chromosomes meet, forming a zygote.
4. Cleavage cell divisions form a morula and then a blastocyst.
5. The outer layer of cells invades and implants in the uterine lining.
6. The inner cell mass develops into the embryo.
7. Certain blastocyst cells secrete hCG.

### The Embryo Forms

During the second week of prenatal development, a space called the amniotic cavity forms between the inner cell mass and the outer cells anchored to the uterine lining. Then the inner cell mass flattens into a two-layered disc. The layer nearest the amniotic cavity is the **ectoderm**; the inner layer, closer to the blastocyst cavity, is the **endoderm**. Shortly after, a third layer, the **mesoderm**, forms in the middle. This three-layered structure is called the primordial embryo, or the **gastrula** (figure 3.15).

Once these three layers, called **primary germ layers**, form, the fates of many cells are determined. This means that they are destined to develop as a specific cell type. Each layer gives rise to certain structures. Cells in



# Bioethics: Choices for the Future

The environment is another powerful factor in why a clone isn't an identical copy. For example, coat color patterns differ in cloned calves and cats. This is because when the animals were embryos, cells destined to produce pigment moved in a unique way in each individual, producing different color patterns. In humans, such factors as experience, nutrition, stress, and exposure to infectious disease join our genes in molding who we are. Identical twins, although they have the same DNA sequence (except for somatic mutations), are not exact replicas of each other. Similarly, cloning a deceased child would probably disappoint parents seeking to recapture their lost loved one.

A compelling argument against reproductive cloning that embraces ethics, biology, and the results of experiments on other animals is that it would likely create an individual who would suffer, because most cloning attempts fail. The reasons may lie in the fact that, as one researcher puts it, "The whole natural order is broken," referring to meiosis, which in the female completes at fertilization. In cloning, a diploid nucleus is introduced into oocyte cytoplasm, where signals direct it to do what a female secondary oocyte tends to do—shed half of itself

as a polar body. If the out-of-place donor nucleus does this, the new cell jettisons half its chromosomes—one genome copy—and becomes haploid. It cannot develop. A final argument against cloning is that it isn't necessary (Figure 1).

The essence of the ethical objection to cloning is that we are dissecting and defining our very individuality, reducing it to a biochemistry so supposedly simple that we can duplicate it. We probably can't.



**Figure 1 Cloned cats.** A company called "Genetic Savings and Clone" tried to sell cloned cats for \$50,000, but lowered the price to only \$32,000 when customers were scarce. The company went out of business in 2006. They never succeeded in cloning dogs, which would have cost \$100,000.

the ectoderm become skin, nervous tissue, or parts of certain glands. Endoderm cells form parts of the liver and pancreas and the linings of many organs. The middle layer of the embryo, the mesoderm, forms many structures, including muscle, connective tissues, the reproductive organs, and the kidneys.

A set of genes called homeotics controls how the embryo develops its parts in the right places. Mutations in these genes cause some very interesting conditions. Figure 16.17 shows one that disrupts hand development. The homeotic mutations were originally studied in fruit flies that had legs growing where their antennae should be. The author did her graduate work on these flies, never suspecting that the mutations had counterparts in humans.

**Table 3.2** summarizes the stages of early prenatal development.

## Supportive Structures Form

As an embryo develops, structures form that support and protect it. These include chorionic villi, the placenta, the yolk sac, the allantois, the umbilical cord, and the amniotic sac.

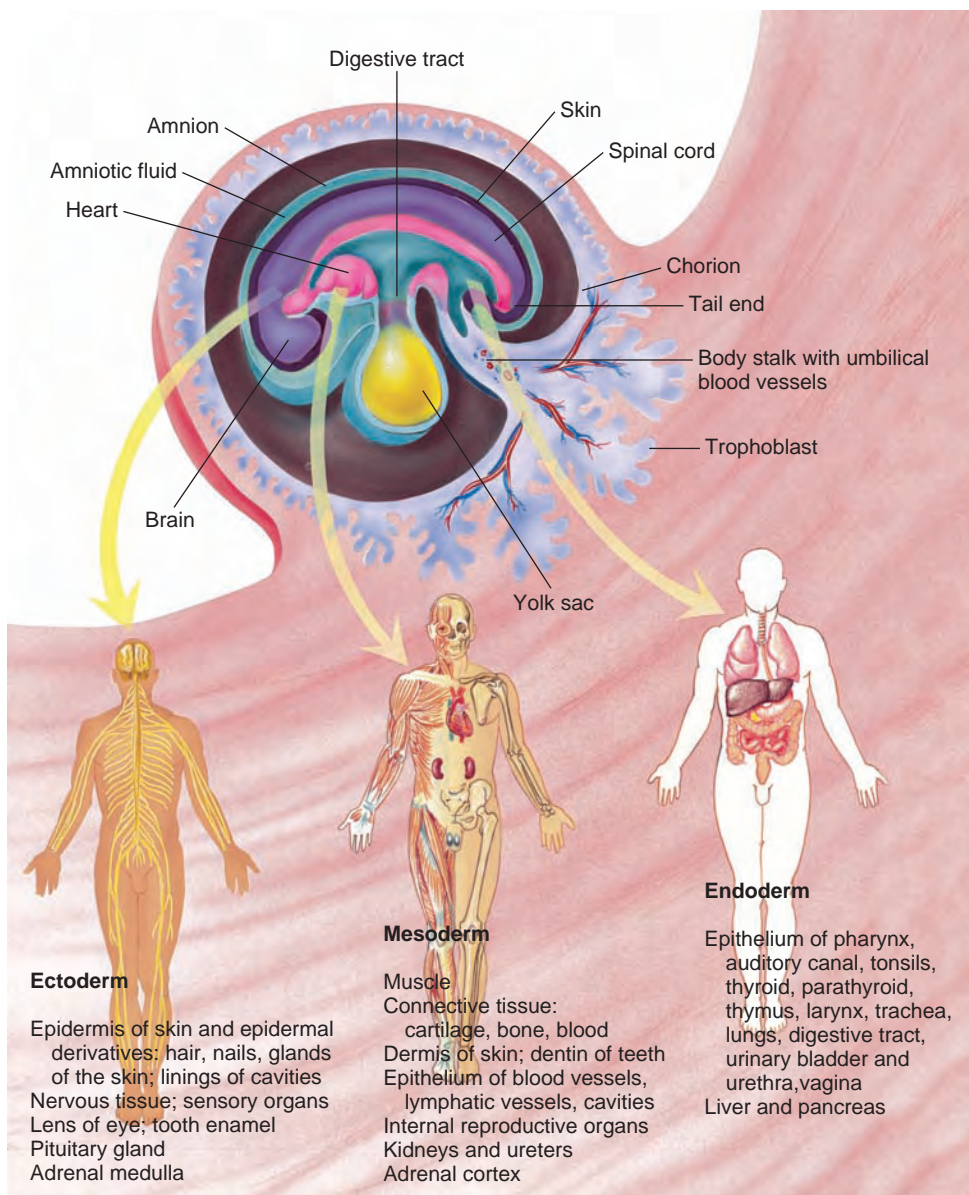
By the third week after conception, finger-like outgrowths called chorionic villi extend from the area of the embryonic disc close to the uterine wall, and these project into pools of the woman's blood. Her blood system and the embryo's are separate, but nutrients and oxygen diffuse across the

chorionic villi from her circulation to the embryo, and wastes leave the embryo's circulation and enter the woman's circulation to be excreted.

By 10 weeks, the placenta is fully formed. It links woman and fetus for the rest of the pregnancy. The placenta secretes hormones that maintain pregnancy and alter the woman's metabolism to send nutrients to the fetus.

Other structures nurture the developing embryo. The yolk sac manufactures blood cells, as does the allantois, a membrane surrounding the embryo that gives rise to the umbilical blood vessels. The umbilical cord forms around these vessels and attaches to the center of the placenta. Toward the end of the embryonic period, the yolk sac shrinks,





**Figure 3.15 The primordial embryo.** When the three basic layers of the embryo form at gastrulation, many cells become “fated” to follow a specific developmental pathway. However, each layer probably retains stem cells as the organism develops. Under certain conditions, these cells may produce daughter cells that can specialize as many cell types.

**Table 3.2**

### Stages and Events of Early Human Prenatal Development

Stage	Time Period	Principal Events
Fertilized ovum	12–24 hours following ovulation	Oocyte fertilized; zygote has 23 pairs of chromosomes and is genetically distinct
Cleavage	30 hours to third day	Mitosis increases cell number
Morula	Third to fourth day	Solid ball of cells
Blastocyst	Fifth day through second week	Hollowed ball forms trophoblast (outside) and inner cell mass, which implants and flattens to form embryonic disc
Gastrula	End of second week	Primary germ layers form

and the amniotic sac swells with fluid that cushions the embryo and maintains a constant temperature and pressure. The amniotic fluid contains fetal urine and cells.

Two of the supportive structures that develop during pregnancy provide the material for prenatal tests (see figure 13.5), discussed in chapter 13. Chorionic villus sampling examines chromosomes from cells snipped off the chorionic villi at 10 weeks. Because the villi cells and the embryo’s cells come from the same fertilized ovum, an abnormal chromosome detected in villi cells should also be in the embryo. In amniocentesis, a sample of amniotic fluid is taken after the fourteenth week of pregnancy, and fetal cells in the fluid are examined for biochemical, genetic, and chromosomal anomalies.

## Key Concepts

1. Germ layers form in the second week. Cells in a specific germ layer later become parts of particular organ systems as a result of differential gene expression.
2. During week 3, chorionic villi extend toward the maternal circulation, and the placenta begins to form.
3. Nutrients and oxygen enter the embryo, and wastes pass from the embryo into the maternal circulation.
4. The yolk sac and allantois manufacture blood cells, the umbilical cord forms, and the amniotic sac expands with fluid.

## Multiples

Twins and other multiples arise early in development. Twins are either fraternal or identical. Fraternal, or **dizygotic** (DZ), twins result when two sperm fertilize two oocytes. This can happen if ovulation occurs in two ovaries in the same month, or if two oocytes leave the same ovary and are both fertilized. DZ twins are no more alike than any two siblings, although they share a very early environment in the uterus. The tendency to have DZ twins may run in families if the women tend to ovulate two oocytes a month.

Identical, or **monozygotic** (MZ), twins descend from a single fertilized ovum and therefore are genetically identical. They are



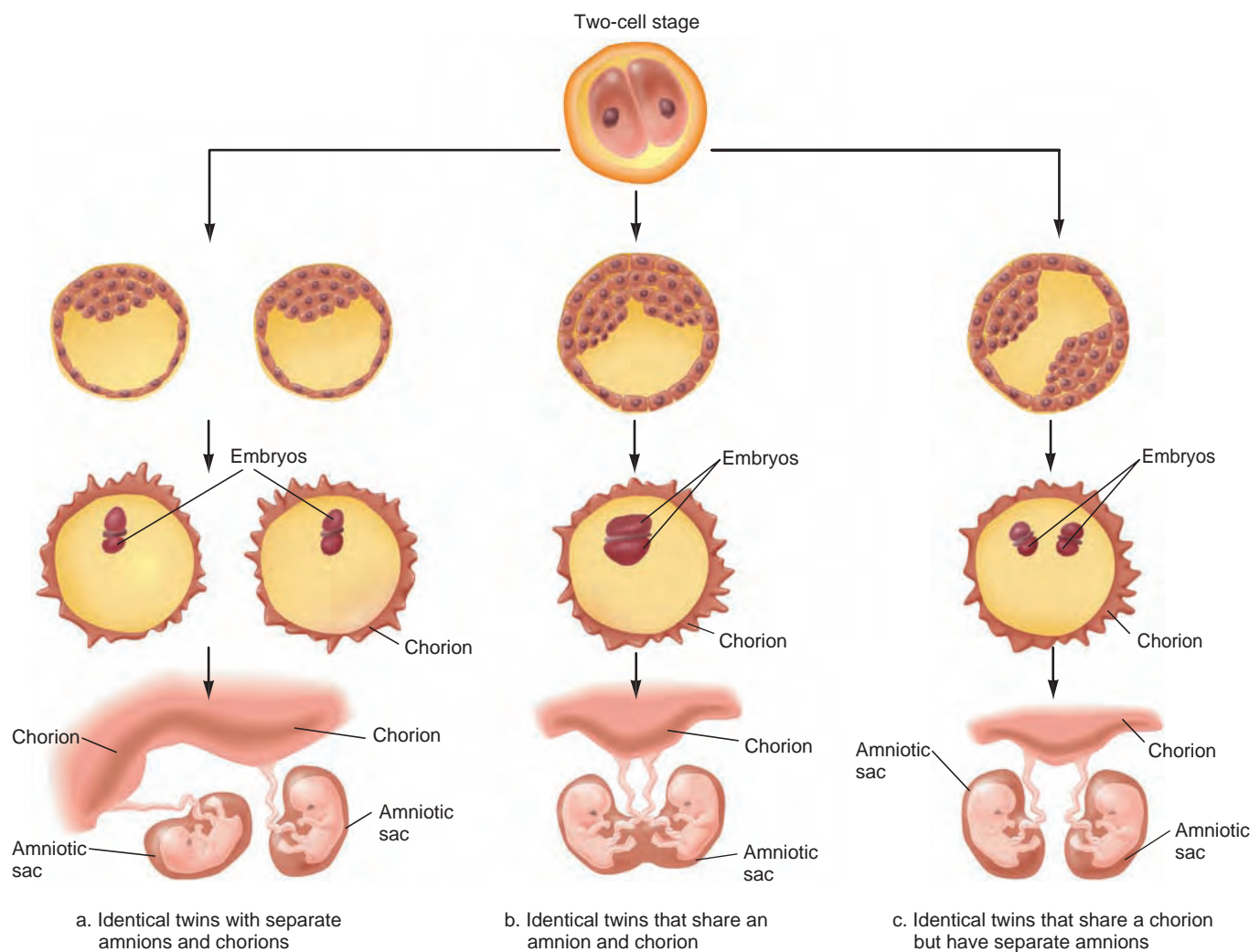
natural clones. Three types of MZ twins can form, depending upon when the fertilized ovum or very early embryo splits (figure 3.16). This difference in timing determines which supportive structures the twins share. About a third of all MZ twins have completely separate chorions and amnions, and about two-thirds share a chorion but have separate amnions. Slightly fewer than 1 percent of MZ twins share both amnion and chorion. (The amnion is the sac that contains fluid that surrounds the fetus. The chorion develops into the placenta.) These differences may expose the different types of MZ twins to slightly different uterine

environments. For example, if one chorion develops more attachment sites to the maternal circulation, one twin may receive more nutrients and gain more weight than the other.

In 1 in 50,000 to 100,000 pregnancies, an embryo divides into twins after the point at which the two groups of cells can develop as two individuals, between days 13 and 15. The result is conjoined or “Siamese” twins. The latter name comes from Chang and Eng Bunker, who were born in Thailand, then called Siam, in 1811. They were joined by a band of tissue from the navel to the breastbone, and could easily have been separated

today. Chang and Eng lived for 63 years, attached. They fathered 22 children and divided each week between their wives.

For Abigail and Brittany Hensel, shown in figure 3.17, the separation occurred after day 9 of development, but before day 14. Biologists know this because the girls’ shared organs have derivatives of ectoderm, mesoderm, and endoderm; that is, when the lump of cells divided incompletely, the three primary germ layers had not yet completely sorted themselves out. The Hensel girls are extremely rare “incomplete twins.” They are “dicephalic,” which means that they have two heads. They are very much individuals.



**Figure 3.16 Types of identical twins.** Identical twins originate at three points in development. **(a)** In about one-third of identical twins, separation of cells into two groups occurs before the trophoblast forms on day 5. These twins have separate chorions and amnions. **(b)** About 1 percent of identical twins share a single amnion and chorion, because the tissue splits into two groups after these structures have already formed. **(c)** In about two-thirds of identical twins, the split occurs after day 5 but before day 9. These twins share a chorion but have separate amnions. Fraternal twins result from two sperm fertilizing two secondary oocytes. These twins develop their own amniotic sacs, yolk sacs, allantois, placentae, and umbilical cords.



**Figure 3.17 Conjoined twins.**

Abby and Brittany Hensel are the result of incomplete twinning during the first two weeks of prenatal development. Brittany is the twin leaning on her elbow.

Each girl has her own neck, head, heart, stomach, gallbladder, and lungs. Each has one leg and one arm, and a third arm between their heads was surgically removed. Each girl also has her own nervous system! The twins share a large liver, a single bloodstream, and all organs below the navel. They have three kidneys. Because at birth Abby and Brittany were strong and healthy, doctors suggested surgery to separate them. But their parents, aware from other cases that only one child would likely survive a separation, chose to let their daughters be.

As teens, Abby and Brittany are glad their parents did not choose to separate them, because they would have been unable to walk or run, as they can today. They enjoy kickball, volleyball, basketball, and cycling. Like any teen girls, they have distinctive tastes in clothing and in food.

MZ twins occur in 3 to 4 pregnancies per 1,000 births worldwide. In North America, twins occur in about 1 in 81 pregnancies, which means that 1 in 40 of us is a twin. However, not all twins survive to be born. One study of twins detected early in pregnancy showed that up to 70 percent of the eventual births are of a single child. This is called the “vanishing twin” phenomenon.

## Key Concepts

1. Dizygotic twins arise from two fertilized ova.
2. Monozygotic twins arise from a single fertilized ovum and may share supportive structures.

## The Embryo Develops

As the days and weeks of prenatal development proceed, different rates of cell division in different parts of the embryo fold the forming tissues into intricate patterns. In a process called embryonic induction, the specialization of one group of cells causes adjacent groups of cells to specialize. Gradually, these changes mold the three primary germ layers into organs and organ systems. Organogenesis is the transformation of the simple three layers of the embryo into distinct organs. During the weeks of organogenesis, the developing embryo is particularly sensitive to environmental influences such as chemicals and viruses.

During the third week of prenatal development, a band called the primitive streak appears along the back of the embryo. The primitive streak gradually elongates to form an axis that other structures organize around as they develop. The primitive streak eventually gives rise to connective tissue precursor cells and the notochord, a structure that forms the basic framework of the skeleton. The notochord induces a sheet of overlying ectoderm to fold into the hollow **neural tube**, which develops into the brain and spinal cord (central nervous system). If the neural tube does not completely zip up by day 20, a birth defect called a neural tube defect (NTD) occurs. As a result, parts of the brain or spinal cord protrude from the open head or spine, and body parts below the defect are not innervated. The person is paralyzed from the point of the NTD down. Some NTDs can be surgically corrected (see the Bioethics Box in Chapter 16). Lack of the B vitamin folic acid can cause NTDs in embryos with a genetic susceptibility. For this reason, the U.S. government supplements grains with the vitamin, and pregnant women take folic acid supplements. A blood test

during the 15th week of pregnancy detects a substance from the fetus’s liver called alpha fetoprotein (AFP) that leaks at an abnormally rapid rate into the woman’s circulation if there is an NTD.

Some nations designate day 14 of prenatal development and primitive streak formation as the point beyond which they ban research on the human embryo. The reason is that the primitive streak is the first sign of a nervous system, and day 14 is also the time at which implantation is complete.

Appearance of the neural tube marks the beginning of organ development. Shortly after, a reddish bulge containing the heart appears. The heart begins to beat around day 18, and this is easily detectable by day 22. Soon the central nervous system starts to form.

The fourth week of embryonic existence is one of spectacularly rapid growth and differentiation (**figure 3.18**). Arms and legs begin to extend from small buds on the torso. Blood cells form and fill primitive blood vessels. Immature lungs and kidneys begin to develop.

By the fifth and sixth weeks, the embryo’s head appears to be too large for the rest of its body. Limbs end in platelike structures with tiny ridges, and gradually apoptosis sculpts the fingers and toes. The eyes are open, but they do not yet have lids or irises. By the seventh and eighth weeks, a skeleton composed of cartilage forms. The embryo is now about the length and weight of a paper clip. At eight weeks of gestation, the prenatal human has rudiments of all of the structures that will be present at birth. It is now a fetus.

## Key Concepts

1. During week 3, the primitive streak appears, followed rapidly by the notochord, neural tube, heart, central nervous system, limbs, digits, facial features, and other organ rudiments.
2. By week 8, all of the organs that will be present in the newborn have begun to develop.



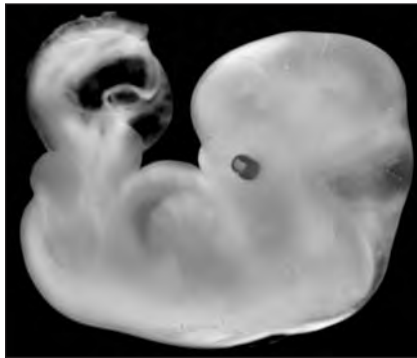
a. 28 days

4–6 mm



c. 56 days

23–32 mm



b. 42 days

12–15 mm

**Figure 3.18 Human embryos.**

Embryos at (a) 28 days, (b) 42 days, and (c) 56 days.

## The Fetus Grows

During the fetal period, body proportions approach those of a newborn (**figure 3.19**). Initially, the ears lie low, and the eyes are widely spaced. Bone begins to replace the softer cartilage. As nerve and muscle functions become coordinated, the fetus moves.

Sex is determined at conception, when a sperm bearing an X or Y chromosome meets an oocyte, which always carries an X chromosome. An individual with two X chromosomes is a female, and one with an X and a Y is a male. A gene on the Y chromosome, called SRY (for “sex-determining region of the Y”), determines maleness.

Differences between the sexes do not appear until week 6, after the SRY gene is expressed in males. Male hormones then stimulate male reproductive organs and glands to differentiate from existing, indifferent structures. In a female, the indifferent structures of the early embryo develop as female organs and glands, under the control of other genes. Differences may be noticeable

on ultrasound scans by 12 to 15 weeks. Sexual development is discussed further in chapter 6.

By week 12, the fetus sucks its thumb, kicks, makes fists and faces, and has the beginnings of teeth. It breathes amniotic fluid in and out, and urinates and defecates into it. The first trimester (three months) of pregnancy ends.

By the fourth month, the fetus has hair, eyebrows, lashes, nipples, and nails. By 18 weeks, the vocal cords have formed, but the fetus makes no sound because it doesn’t breathe air. By the end of the fifth month, the fetus curls into a head-to-knees position. It weighs about 454 grams (1 pound). During the sixth month, the skin appears wrinkled because there isn’t much fat beneath it, and turns pink as capillaries fill with blood (**figure 3.19**). By the end of the second trimester, the woman feels distinct kicks and jabs and may even detect a fetal hiccup. The fetus is now about 23 centimeters (9 inches) long.

In the final trimester, fetal brain cells rapidly link into networks as organs elabo-

rate and grow. A layer of fat forms beneath the skin. The digestive and respiratory systems mature last, which is why infants born prematurely often have difficulty digesting milk and breathing. Approximately 266 days after a single sperm burrowed its way into an oocyte, a baby is ready to be born.

The birth of a live, healthy baby is against the odds. Of every 100 secondary oocytes exposed to sperm, 84 are fertilized. Of these 84, 69 implant in the uterus, 42 survive one week or longer, 37 survive six weeks or longer, and only 31 are born alive. Of the fertilized ova that do not survive, about half have chromosomal abnormalities that cause problems too severe for development to proceed.



**Figure 3.19 A fetus at 24 weeks.** At this stage and beyond, a fetus can survive outside of the uterus—but many do not.

## Key Concepts

1. During the fetal period, structures grow, specialize, and begin to interact.
2. Bone replaces cartilage in the skeleton, body growth catches up with the head, and sex organs become more distinct.
3. In the final trimester, the fetus moves and grows rapidly, and fat fills out the skin.



3.5 Birth Defects

When genetic abnormalities or toxic exposures affect an embryo or fetus, developmental problems occur, resulting in birth defects. Only a genetically caused birth defect can be passed to future generations. Although development can be derailed in many ways, about 97 percent of newborns appear healthy at birth.

The Critical Period

The specific nature of a birth defect usually depends on which structures are developing when the damage occurs. The time when genetic abnormalities, toxic substances, or viruses can alter a specific structure is its **critical period** (figure 3.20). Some body parts, such as fingers and toes, are sensitive for short periods of time. In contrast, the brain is sensitive throughout prenatal development, and connections between nerve cells continue to change throughout life. Because of the brain’s continuous critical period, many birth defect syndromes include learning disabilities or mental retardation.

About two-thirds of all birth defects arise from a disruption during the embryonic period. More subtle defects, such as learning disabilities, that become noticeable only after infancy are often caused by interventions during the fetal period. A disruption in the first trimester might cause mental retardation; in the seventh month of pregnancy, it might cause difficulty in learning to read.

Some birth defects can be attributed to an abnormal gene that acts at a specific point in prenatal development. In a rare inherited condition called phocomelia (OMIM 276826), for example, a mutation halts limb development from the third to the fifth week of the embryonic period, causing “flippers” to develop in place of arms and legs. The risk that a genetically caused birth defect will affect a particular family member can be calculated.

Many birth defects are caused not by mutant genes but by toxic substances the pregnant woman encounters. These environmentally caused problems will not affect another family member unless the exposure occurs again. Chemicals or other

agents that cause birth defects are called **teratogens** (Greek for “monster-causing”). While it is best to avoid teratogens while pregnant, some women may need to remain on potentially teratogenic drugs to maintain their own health.

Teratogens

Most drugs are not teratogens. Whether or not exposure to a particular drug causes birth defects may depend upon a woman’s genes. For example, certain variants of a gene that control the body’s use of an amino acid called homocysteine affect whether or not the medication valproic acid causes birth defects. Valproic acid is used to prevent seizures and symptoms of bipolar disorder. Rarely, it can cause NTDs, heart defects, hernias, and club foot. Women can be tested for this gene variant (*MTHFR C677T*, OMIM 607093) and if they have it, switch to a different medication when they try to conceive.

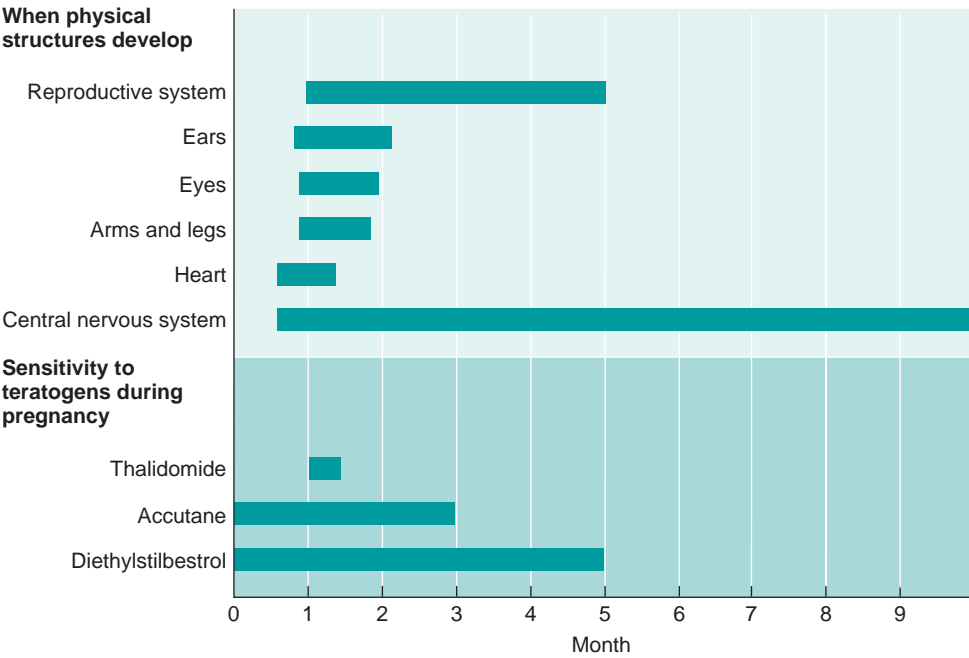
Thalidomide

The idea that the placenta protects the embryo and fetus against harmful substances was tragically disproven between 1957 and 1961, when 10,000 children were born in Europe with what seemed, at first, to be phocomelia. Because doctors realized that this genetic disorder is very rare, they began to look for another cause. They soon discovered that the mothers had all taken a mild tranquilizer to alleviate nausea, thalidomide, early in pregnancy, during the time an embryo’s limbs form. Many “thalidomide babies” were born with incomplete or missing legs and arms.

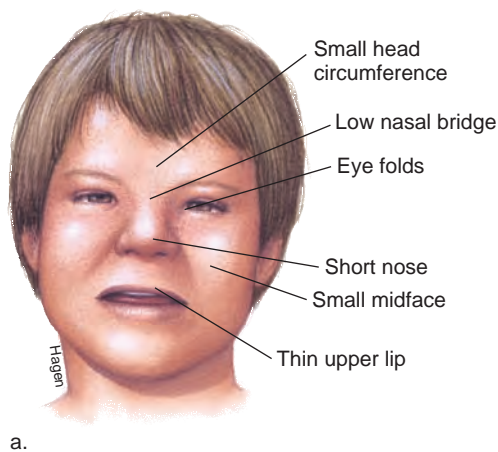
The United States was spared from the thalidomide disaster because an astute government physician noted the drug’s adverse effects on laboratory monkeys. Still, several “thalidomide babies” were born in South America in 1994, where pregnant women were given the drug. In spite of its teratogenic effects, thalidomide is a valuable drug. It is used to treat leprosy, AIDS, and certain blood and bone marrow cancers.

Cocaine

Cocaine can cause spontaneous abortion by inducing a stroke in the fetus. Cocaine-exposed infants are distracted and unable to



**Figure 3.20 Critical periods of development.** The nature of a birth defect resulting from drug exposure depends upon which structures were developing at the time of exposure. The time when a particular structure is vulnerable is called its critical period. Accutane is an acne medication that causes cleft palate and eye, brain, and heart defects. Diethylstilbestrol (DES) was used in the 1950s to prevent miscarriage. It caused vaginal cancer in some “DES daughters.” Thalidomide was used to prevent morning sickness.



b.



c.



d.

**Figure 3.21 Fetal alcohol syndrome.** Some children whose mothers drank alcohol during pregnancy have characteristic flat faces (**a**) that are strikingly similar in children of different races (**b**, **c**, and **d**).

concentrate on their surroundings. Other health and behavioral problems arise as these children grow.

One problem in evaluating the prenatal effects of cocaine is that affected children are often exposed to other environmental influences that could account for their symptoms. Cocaine use by a father can affect an embryo because the cocaine binds to sperm.

## Cigarettes

Chemicals in cigarette smoke stress a fetus. Carbon monoxide crosses the placenta and prevents the fetus's hemoglobin molecules from adequately binding oxygen. Other chemicals in smoke block nutrients. Smoke-exposed placentas lack important growth factors, causing poor growth before and after birth. Cigarette smoking during pregnancy increases the risk of spontaneous abortion, stillbirth, prematurity, and low birth weight.

## Alcohol

A pregnant woman who has just one or two alcoholic drinks a day, or perhaps a large amount at a single crucial time, risks fetal alcohol syndrome (FAS) in her unborn child. Tests for gene variants that encode proteins that regulate alcohol metabolism may be able to predict which women and fetuses are at elevated risk for developing FAS, but until these tests are marketed, pregnant women are advised to avoid all alcohol.

A child with FAS has a characteristic small head and a flat face (**figure 3.21**). Growth is slow before and after birth. Intellectual impairment ranges from minor learning disabilities to mental retardation. Teens and young adults who have FAS are short and have small heads. More than 80 percent of them retain the facial characteristics of a young child with FAS.

The long-term mental effects of prenatal alcohol exposure are more severe than the physical vestiges. Many adults with FAS function at early grade-school level. They often lack social and communication skills and find it difficult to understand the consequences of actions, form friendships, take initiative, and interpret social cues.

Aristotle noticed problems in children of alcoholic mothers more than 23 centuries ago. In the United States today, 1 to 3 of every 1,000 infants has the syndrome, meaning 2,000 to 6,000 affected children are born each year. Many more children have milder "alcohol-related effects." A fetus of a woman with active alcoholism has a 30 to 45 percent chance of harm from prenatal alcohol exposure.

## Nutrients

Certain nutrients ingested in large amounts, particularly vitamins, act as drugs. The acne medicine isotretinoin (Accutane) is a vitamin A derivative that causes spontaneous abortion and defects of the heart, nervous system, and face in exposed embryos. Physicians first noted the tragic effects of

this drug nine months after dermatologists began prescribing it to young women in the early 1980s. Another vitamin A-based drug, used to treat psoriasis, as well as excesses of vitamin A itself, also cause birth defects. Some forms of vitamin A are stored in body fat for up to three years.

Excess vitamin C can harm a fetus if it becomes accustomed to the large amounts the woman takes. After birth, when the vitamin supply suddenly plummets, the baby may develop symptoms of vitamin C deficiency (scurvy), bruising and becoming infected easily.

Malnutrition threatens a fetus. A woman must consume extra calories while she is pregnant or breastfeeding. Obstetrical records of pregnant women before, during, and after World War II link inadequate nutrition in early pregnancy to an increase in the incidence of spontaneous abortion. The aborted fetuses had very little brain tissue. Poor nutrition later in pregnancy affects the development of the placenta and can cause low birth weight, short stature, tooth decay, delayed sexual development, and learning disabilities.

## Occupational Hazards

Teratogens are present in some workplaces. Researchers note increased rates of spontaneous abortion and children born with birth defects among women who work with textile dyes, lead, certain photographic chemicals, semiconductor materials, mercury, and cadmium. Men whose jobs expose them

to sustained heat, such as smelter workers, glass manufacturers, and bakers, may produce sperm that can fertilize an oocyte and then cause spontaneous abortion or a birth defect. A virus or a toxic chemical carried in semen may also cause a birth defect.

## Viral Infection

Viruses are small enough to cross the placenta and reach a fetus. Some viruses that cause mild symptoms in an adult, such as the chickenpox virus, may devastate a fetus. Men can transmit viral infections to an embryo or fetus during sexual intercourse.

HIV can reach a fetus through the placenta or infect a newborn via blood contact during birth. Fifteen to 30 percent of infants born to untreated HIV-positive women are HIV positive. The risk of transmission is significantly reduced if a pregnant woman takes anti-HIV drugs. All fetuses of HIV-infected women are at higher risk for low birth weight, prematurity, and stillbirth if the woman's health is failing.

German measles (rubella) is a well-known viral teratogen. In the United States, in the early 1960s, an epidemic of the usually mild illness caused 20,000 birth defects and 30,000 stillbirths. Children who were exposed during the first trimester of pregnancy could develop cataracts, deafness, and heart defects. Fetuses exposed during the second or third trimesters of pregnancy may have as a result developed learning disabilities, speech and hearing problems, and type 1 diabetes mellitus.

The incidence of these problems, called congenital rubella syndrome, has dropped markedly since vaccination eliminated the disease in the United States. However, the syndrome resurfaces in unvaccinated populations. In 1991 among a cluster of unvaccinated Amish women in rural Pennsylvania, 14 of every 1,000 newborns had congenital rubella syndrome, compared to an incidence then of 0.006 per 1,000 in the general U.S. population.

Herpes simplex virus can harm a fetus or newborn whose immune system is immature. Forty percent of babies exposed to active vaginal herpes lesions become infected, and half of them die. Of the survivors, 25 percent sustain severe nervous system damage, and another 25 percent have skin sores. A surgical delivery can protect the child.

Pregnant women are routinely checked for hepatitis B infection, which in adults causes liver inflammation, great fatigue, and other symptoms. Each year in the United States, 22,000 infants are infected with this virus during birth. These babies are healthy, but at high risk for developing serious liver problems as adults. When infected women are identified, a vaccine can be given to their newborns to help prevent complications.

## Key Concepts

1. The critical period is the time during prenatal development when a structure is sensitive to damage from a faulty gene or environmental insult.
2. Most birth defects develop during the embryonic period and are more severe than problems that arise during fetal development.
3. Teratogens are agents that cause birth defects.

## 3.6 Maturation and Aging

“Aging” means moving through the life cycle, and it begins at conception. In adulthood, as we age, the limited life spans of cells are reflected in the waxing and waning of biological structures and functions. Although some aspects of our anatomy and physiology peak very early—such as the number of brain cells or hearing acuity, which do so in childhood—age 30 seems to be a turning point for decline. Some researchers estimate that, after this age, the human body becomes functionally less efficient by about 0.8 percent each year.

Many diseases that begin in adulthood, or are associated with aging, have genetic components. Often these disorders are multifactorial, because it takes many years for environmental exposures to alter gene expression in ways that noticeably affect health. Following is a closer look at how genes may impact health throughout life.

## Adult-Onset Inherited Disorders

Human prenatal development is a highly regulated program of genetic switches that are turned on in specific body parts at

specific times. Environmental factors can affect how certain genes are expressed before birth in ways that create risks that appear much later. Specifically, adaptations that enable a fetus to grow despite near-starvation become risk factors for certain common conditions of adulthood, such as coronary artery disease, obesity, stroke, hypertension, and type 2 diabetes mellitus. A fetus that does not receive adequate nutrition has intrauterine growth retardation (IUGR), and though born on time, is very small. Premature infants, in contrast, are small but are born early, and are not predisposed to conditions resulting from IUGR.

More than one hundred studies clearly correlate low birth weight due to IUGR with increased incidence of cardiovascular disease later in life. Much of the data come from war records because enough time has elapsed to study the effects of prenatal malnutrition as people age. For example, a study of nearly 15,000 people born in Sweden from 1915 to 1929 correlates IUGR to heightened cardiovascular disease risk after age 65. Similarly, an analysis of individuals who were fetuses during a seven-month famine in the Netherlands in 1943 indicates a high rate of diabetes among them today. Experiments on intentionally starved sheep and rat fetuses support these historical findings.

How can poor nutrition before birth cause disease decades later? Perhaps to survive, the starving fetus redirects its circulation to protect vital organs such as the brain. At the same time, muscle mass and hormone production change to conserve energy. Growth-retarded babies have too little muscle tissue, and since muscle is the primary site of insulin action, glucose metabolism is altered. Thinness at birth, and the accelerated weight gain in childhood that often occurs to compensate, sets the stage for coronary heart disease and type 2 diabetes much later.

In contrast to the delayed effects of fetal malnutrition, symptoms of single gene disorders can begin at any time (**Table 3.3**). In general, inherited conditions that affect children are recessive. A fetus who has inherited osteogenesis imperfecta (“brittle bone disease”, OMIM 166210), for example, may already have broken bones (**figure 3.22a**). Most dominantly inherited conditions start to affect health in early to middle adulthood. This is the case for polycystic kidney



Table 3.3

## Time of Onset of Genetic Disorders

Prenatal Period	Birth	10 Years	20 Years	30 Years	40 Years	50 Years
Osteogenesis imperfecta	Adrenoleukodystrophy	Familial hypertrophic cardiomyopathy	Multiple endocrine neoplasia	Hemochromatosis	Gout	Fatal familial insomnia
Pituitary dwarfism	Chronic granulomatous disease	Wilson disease	Marfan syndrome	Breast cancer	Huntington disease	Alzheimer disease
Lissencephaly	von Willebrand disease			Polycystic kidney disease	Pattern baldness	Porphyria
Wilms' tumor	Xeroderma pigmentosum					Amyotrophic lateral sclerosis
Polydactyly	Diabetes insipidus					
	Colorblindness					
	Familial hypercholesterolemia					
	Albinism					
	Duchenne muscular dystrophy					
	Menkes disease					
	Sickle cell disease					
	Rickets					
	Cystic fibrosis					
	Hemophilia					
	Tay-Sachs disease					
	Phenylketonuria					
	Progeria					

disease (OMIM 173900). Cysts that may have been present but undetected in the kidneys during one's twenties begin causing bloody urine, high blood pressure, and abdominal pain in the thirties. Similarly, the joint destruction of osteoarthritis may begin in one's thirties, but not cause pain for twenty years. The uncontrollable movements, unsteady gait, and diminishing mental faculties of Huntington disease typically begin near age 40 or later.

Five to 10 percent of Alzheimer disease cases are inherited and produce initial symptoms in the forties and fifties. German neurologist Alois Alzheimer first identified the condition in 1907 as affecting people in mid-adulthood. Noninherited Alzheimer disease typically begins later in life (figure 3.22b).

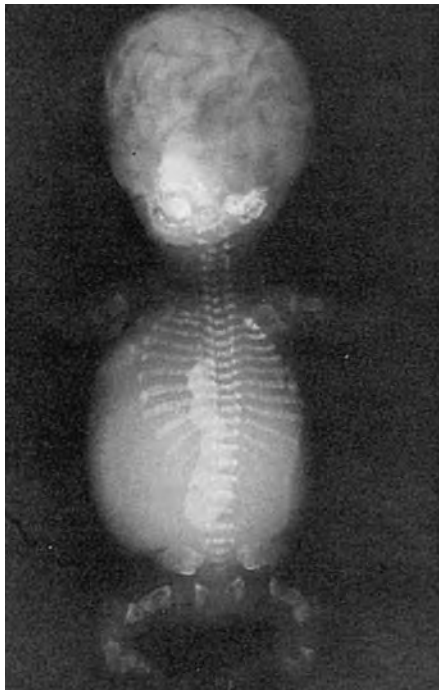
Whatever the age of onset, Alzheimer disease starts gradually. Mental function declines steadily for three to ten years after the first symptoms appear. Confused and forgetful, Alzheimer patients often wander away from family and friends. Finally, the patient cannot perform basic functions such as speaking or eating and usually must be cared for in a hospital or nursing home.

On autopsy, the brains of Alzheimer disease patients are found to contain deposits of a protein called beta amyloid in learning and memory centers. Alzheimer brains also contain structures called neurofibrillary tangles, which consist of a protein called tau. Tau binds to and disrupts microtubules in nerve cell branches, destroying the shape of the cell, which is essential to its ability to communicate.

## Disorders That Resemble Accelerated Aging

Genes control aging both passively (as structures break down) and actively (by initiating new activities). A group of "rapid aging" inherited disorders may hold clues to how genes control aging. It isn't clear whether these conditions actually speed aging, or produce symptoms that resemble those more common in older people.

The most severe rapid aging disorders are the segmental progeroid syndromes. (They were once called progerias, but the newer terminology reflects the fact that they do not hasten all aspects of aging.) Most of these disorders, possibly all, are caused by cells' inability to adequately repair DNA. This enables mutations that would ordinarily



a.



b.

**Figure 3.22 Genes act at various stages of development and life.**

**(a)** Osteogenesis imperfecta breaks bones, even before birth. This fetus has broken limb bones, a beaded appearance of the ribs due to fractures, and a poorly mineralized skull. **(b)** At the funeral of former president Richard M. Nixon in April 1994, all was not right with former president Ronald Reagan. He was forgetful and responded inappropriately to questions. Six months later he penned a moving letter confirming that he had Alzheimer disease. By 1997, Reagan no longer knew the names of his closest relatives. By 1999, he didn't remember anyone, and by 2001 he no longer recalled being president. He died in June 2004. Because of the late onset of symptoms, Ronald Reagan's Alzheimer disease is probably not due to the malfunction of a single gene, but is multifactorial.

**Table 3.4**

### Rapid Aging Syndromes

Disorder	Incidence	Average Life Span	OMIM Number
Ataxia telangiectasia	1/60,000	20	208900
Cockayne syndrome	1/100,000	20	216400
Hutchinson-Gilford syndrome	<1/1,000,000	13	176670
Rothmund-Thomson syndrome	<1/100,000	normal	268400
Trichothiodystrophy	<1/100,000	10	601675
Werner syndrome	<1/100,000	50	277700

be corrected to persist. Over time, the accumulation of mutations destabilizes the entire genome, and even more mutations occur in somatic cells. The various changes that we associate with aging occur.

**Table 3.4** lists the more common segmental progeroid syndromes. They vary in severity. People with Rothmund-Thomson syndrome, for example, may have a normal life span, but develop gray hair or bald-

ness, cataracts, cancers, and osteoporosis at young ages. The child in **figure 3.23**, in contrast, shows the extremely rapid course of Hutchinson-Gilford syndrome. An affected child appears normal at birth but slows in growth by the first birthday. Within just a few years, the child becomes wrinkled and bald, with the facial features characteristic of advanced age. The body ages on the inside as well, as arteries clog with fatty deposits. The child usually dies of a heart attack or a stroke by age 13, although some patients live into their twenties. Only a few dozen cases of this syndrome have ever been reported.

Werner syndrome becomes apparent before age 20, causing death before age 50 from diseases associated with aging. Young adults with Werner syndrome develop atherosclerosis, type 2 diabetes mellitus, hair graying and loss, osteoporosis, cataracts, and wrinkled skin. They are short because they skip the growth spurt of adolescence.

Not surprisingly, the cells of segmental progeroid syndrome patients show aging-related changes. Normal cells growing in culture divide about 50 times before dying. Cells from progeroid syndrome patients die in culture after only 10 to 30 divisions. Understanding how and why these cells seem to race through the aging process may help us to understand genetic control of normal aging.

## Is Longevity Inherited?

Aging reflects genetic activity plus a lifetime of environmental influences. Families with many very aged members have a fortuitous collection of genes plus shared environmental influences such as good nutrition, excellent health care, devoted relatives, and other advantages. A genome-level approach to identifying causes of longevity identified a region of chromosome 4 that houses gene variants associated with long life. Genome comparisons among people who've passed their 100th birthdays and those who have died of the common illnesses of older age will reveal other genes that influence longevity (**Reading 3.1**).

It is difficult to tease apart inborn from environmental influences on life span. One approach compares adopted individuals to both their biological and adoptive parents. In a study from Denmark, adopted



## Reading 3.1

### The Centenarian Genome

The human genome is like a vast library that holds the clues to good health. One way to identify those clues is to probe the genomes of those who have lived the longest, past 100 years. These fortunate people are called centenarians (**Figure 1**). Usually they enjoy excellent health, remaining active and interested in community affairs, then succumb rapidly to a disease that usually claims people decades earlier.

Centenarians fall into three broad groups—about 20 percent of them never get the diseases that kill most people; 40 percent get these diseases, but at a much older age than average; and the other 40 percent live with and survive the more

common disorders of aging. Researchers hope that learning which gene variants offer this protection will lead to better understanding of the common disorders of later adulthood—heart disease, stroke, cancers, type 2 diabetes mellitus, and dementias.

While the environment seems to play an important role in the deaths of people ages 60 to 85, past that age, genes predominate. That is, someone who dies at age 68 of lung cancer can probably blame a lifetime of cigarette smoking. But a smoker who dies at age 101 of the same disease probably had gene variants that protected against lung cancer. Centenarians have higher levels of large lipoproteins that carry cholesterol (HDL) than other people, which researchers estimate adds 20 years of life.

Evidence that longevity is largely inherited is that children and siblings of centenarians tend to be long-lived as well. Brothers of centenarians are 17 times as likely to live past age 100 as the average man, and sisters are 8.5 times as likely. The fact that some people more than 100 years of age have less-than-healthy habits suggests that genes are protecting them. One researcher suggests that the saying, “The older you get, the sicker you get” be replaced with “The older you get, the healthier you’ve been.”

Centenarians have luckily inherited two types of gene variants—those that directly protect them, and wild type alleles of genes that, when mutant, cause disease. Research focuses on individual genes as well as genomewide scans to identify gene variants that make it more likely that a person will live past age 100. **Table 1** lists some “candidate” gene types that may control longevity. To find other gene variants that promote long life, researchers are comparing the genomes of centenarians with those of

people with particular conditions associated with aging. For example, a group of these very old people all have certain gene variants that differ from those in people with type 2 diabetes mellitus, suggesting that these DNA sequences may protect against deranged glucose metabolism.

Several studies are identifying gene variants that contribute to living long and well. The New England Centenarian Study, headed at Boston University, began in 1988 to amass information on families of the oldest citizens in the United States. The researchers are compiling a “healthy standard genome.” Investigators from the Coriell Institute in New Jersey are probing the genomes of people over age 90 who live in nursing homes. So far, what these people have in common, besides never having had heart disease, is never having smoked. Several had cancer, indicating that cancers are often survivable. Researchers at the University of Pittsburgh have identified places in the genome that harbor “successful aging genes” that have variants that preserve cognition. Perhaps these studies will provide information that will help the majority of us who have not been fortunate enough to have inherited longevity gene variants.



**Figure 1** This woman has enjoyed living for more than a century. Researchers are discovering clues to good health by probing the genomes of centenarians.

**Table 1**

Single genes important in aging affect:

- control of insulin secretion and glucose metabolism.
- immune system functioning.
- control of the cell cycle.
- lipid (cholesterol) metabolism.
- response to stress.
- production of antioxidant enzymes.





**Figure 3.23 Segmental progeroid syndromes.** This child has Hutchinson-Gilford syndrome, which is extremely rare.

individuals with one biological parent who died of natural causes before age 50 were more than twice as likely to die before age 50 as were adoptees whose biological parents lived beyond this age, suggesting an inherited

component to longevity. Interestingly, adopted individuals whose natural parents died early due to infection were more than five times as likely to also die early of infection, perhaps because of inherited immune

system deficiencies. The adoptive parents' ages at death had no influence on that of their adopted children. Chapter 7 explores the "nature versus nurture" phenomenon more closely.

## Key Concepts

1. Starvation before birth can set the stage for later disease by affecting gene expression in certain ways.
2. Most single-gene disorders are recessive and strike early in life. Single-gene disorders with an adult onset are more likely to be dominant.
3. The segmental progeroid syndromes are single-gene disorders that speed the signs of aging.
4. Families with many aged members can thank their genes as well as the environment. Chromosome 4 houses longevity genes, and genome-wide screens are identifying others.
5. Adoption studies compare the effects of genes versus environmental influences on longevity.

## Summary

### 3.1 The Reproductive System

1. The male and female reproductive systems include paired **gonads** and networks of tubes in which **sperm** and **oocytes** are manufactured.
2. Male **gametes** originate in seminiferous tubules within the paired testes. They then pass through the epididymis and vasa deferentia, where they mature before exiting the body through the urethra during sexual intercourse. The prostate gland, the seminal vesicles, and the bulbourethral glands add secretions.
3. Female gametes originate in the ovaries. Each month after puberty, one ovary releases an oocyte into a uterine tube. The oocyte then moves to the uterus for implantation (if fertilized) or expulsion.

### 3.2 Meiosis

4. **Meiosis** reduces the chromosome number in gametes to one genome, from **diploid** to **haploid**. This maintains the

chromosome number from generation to generation. Meiosis ensures genetic variability by **independently assorting** different combinations of genes into gametes as a result of random alignment of chromosomes and **crossing over**.

5. Meiosis I, **reduction division**, halves the number of chromosomes. Meiosis II, **equational division**, produces four cells from the two that result from meiosis I, without another DNA replication.
6. Crossing over occurs during prophase I. It mixes up paternally and maternally derived genes on **homologous pairs** of chromosomes.
7. Chromosomes segregate and independently assort in metaphase I, which determines the distribution of genes from each parent.

### 3.3 Gamete Maturation

8. **Spermatogenesis** begins with spermatogonia, which accumulate

cytoplasm and replicate their DNA, becoming primary spermatocytes. After meiosis I, the cells become haploid secondary spermatocytes. In meiosis II, the secondary spermatocytes divide, each yielding two spermatids, which then differentiate into spermatozoa.

9. In **oogenesis**, some oogonia grow and replicate their DNA, becoming primary oocytes. In meiosis I, the primary oocyte divides to yield one large secondary oocyte and a much smaller **polar body**. In meiosis II, the secondary oocyte divides to yield the large ovum and another small polar body. Female meiosis is completed at fertilization.

### 3.4 Prenatal Development

10. In the female, sperm are capacitated and drawn toward a secondary oocyte. One sperm burrows through the oocyte's protective layers with acrosomal enzymes. Fertilization occurs when the sperm and oocyte fuse and their DNA combines

in one nucleus, forming the **zygote**. Electrochemical changes in the egg surface block additional sperm from entering. **Cleavage** begins and a 16-celled **morula** forms. Between days 3 and 6, the morula arrives at the uterus and hollows, forming a **blastocyst** made up of **blastomeres**. The trophoblast and **inner cell mass** form. Around day 6 or 7, the blastocyst implants, and trophoblast cells secrete hCG, which prevents menstruation.

11. During the second week, the amniotic cavity forms as the inner cell mass flattens. **Ectoderm** and **endoderm** form, and then **mesoderm** appears, establishing the **primary germ layers**. Cells in each germ layer begin to develop into specific organs. During the third week, the placenta, yolk sac, allantois, and umbilical cord begin to form as the amniotic cavity swells with fluid. **Monozygotic** twins result when one fertilized ovum splits. **Dizygotic** twins result from two fertilized ova. Organs

form throughout the embryonic period. Structures including the primitive streak, the notochord and **neural tube**, arm and leg buds, the heart, facial features, and the skeleton gradually appear.

12. At the eighth week, the **embryo** becomes a **fetus**, with all structures present but not fully grown. Organ rudiments laid down in the embryo grow and specialize. The developing organism moves and reacts, and gradually, its body proportions resemble those of a baby. In the last trimester, the brain develops rapidly, and fat is deposited beneath the skin. The digestive and respiratory systems mature last.

### 3.5 Birth Defects

13. Birth defects can result from a mutation or an environmental intervention.
14. A substance that causes birth defects is a **teratogen**. Environmentally caused birth

defects are not transmitted to future generations.

15. The time when a structure is sensitive to damage from an abnormal gene or environmental intervention is its **critical period**.

### 3.6 Maturation and Aging

16. Genes cause or predispose us to illness throughout life. Single-gene disorders that strike early tend to be recessive; most adult-onset single-gene conditions are dominant.
17. Malnutrition before birth can alter gene expression in ways that cause illness later in life.
18. The segmental progeroid syndromes are single-gene disorders that increase the rate of aging-associated changes.
19. Long life is due to genetics and environmental influences.

## Review Questions

1. How many sets of human chromosomes are in each of the following cell types?
  - a. an oogonium
  - b. a primary spermatocyte
  - c. a spermatid
  - d. a cell from either sex during anaphase of meiosis I
  - e. a cell from either sex during anaphase of meiosis II
  - f. a secondary oocyte
  - g. a polar body derived from a primary oocyte
2. List the structures and functions of the male and female reproductive systems.
3. A dog has 39 pairs of chromosomes. Considering only the random alignment

of chromosomes, how many genetically different puppies are possible when two dogs mate? Is this number an underestimate or overestimate of the actual total? Why?

4. How does meiosis differ from mitosis?
5. What do oogenesis and spermatogenesis have in common, and how do they differ?
6. How does gamete maturation differ in the male and female?
7. Why is it necessary for spermatogenesis and oogenesis to generate stem cells?
8. Describe the events of fertilization.
9. Write the time sequence in which the following structures begin to develop: notochord, gastrula, inner cell mass, fetus, zygote, morula.

10. Exposure to teratogens tends to produce more severe health effects in an embryo than in a fetus. Why?
11. The same birth defect syndrome can be caused by a mutant gene or exposure to a teratogen. How do the consequences of each cause differ for future generations?
12. List four teratogens, and explain how they disrupt prenatal development.
13. Why is an “anti-aging” pill, diet, or contraption impossible?
14. Cite two pieces of evidence that genes control aging.

## Applied Questions

1. Up to what stage, if any, do you think it is ethical to experiment on a prenatal human? Cite reasons for your answer.
2. Under a microscope, a first and second polar body look alike. What structure would distinguish them?

3. Armadillos always give birth to identical quadruplets. Are the offspring clones?
4. Some Vietnam War veterans who were exposed to the herbicide Agent Orange claim that their children—born years after the exposure—have birth defects caused

by dioxin, a contaminant in the herbicide. What types of cells would the chemical have to have affected in these men to cause birth defects years later?

5. In about 1 in 200 pregnancies, a sperm fertilizes a polar body instead of an oocyte.

A mass of tissue that is not an embryo develops. Why can't a polar body support the development of an entire embryo?

6. Should a woman be held legally responsible if she drinks alcohol, smokes, or abuses drugs during pregnancy and it harms her child? Should liability apply to all substances that can harm a fetus, or only to those that are illegal?
7. Would you want to one day have your genome scanned to estimate how long you are likely to live? Why or why not?
8. What types of evidence have led researchers to hypothesize that a poor prenatal environment can raise the risk for certain adult illnesses? How are genes part of this picture?

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 3** and **Web Activities** to find the website links needed to complete the following activities.

9. Look over the “Living to 100 life expectancy calculator” at the website provided on the OLC and list ten ways that you can change your behavior to possibly live longer. What does this quiz suggest about the relative role of genes and the environment in determining longevity?
10. Go to the website provided on the OLC and look at the photographs of Lily, Daffodil, Crocus, Forsythia, and Rose. What is the evidence that these calf clones are not identical?
11. Go to the Motherisk website at <http://www.motherisk.org/>. Click on “Women, Partners, Family and Friends.” Then click on “drugs in pregnancy” in the left-hand list. Identify three drugs that are safe to take during pregnancy and three that are not safe, and list the associated medical problems.

## Case Studies and Research Results

12. Miguel and Maria are carriers of cystic fibrosis (CF), and the condition is severe in their families. They have a procedure called preimplantation genetic diagnosis (see figure 21.5) to ensure that their child does not inherit CF. Maria's oocyte is fertilized with Miguel's sperm in a laboratory dish, and it develops to the 8-cell stage. One cell is removed and tested for the mutant allele that is on both sides of the family. Only the wild type allele is detected.

Anna and Peter are also carriers of a genetic disorder that can affect either sex. They cannot get into a preimplantation genetic diagnosis clinical trial, which would be free; their insurance will not cover the procedure; and they cannot afford it. So, they choose chorionic villus sampling (CVS), in which a cell from the developing placenta is tested for the mutant allele. CVS is done at the tenth week of gestation. Their fetus is found to be a carrier, like them.

A third couple, Vivian and Max, are not willing to take the higher risk of miscarriage associated with CVS, so they wait until the sixteenth week, and Vivian has amniocentesis. Fetal cells are sampled from the amniotic fluid and the mutation that causes the clotting disorder hemophilia in Vivian's family checked. Vivian may be a carrier for hemophilia A. If she is, a son would face a 50 percent chance of inheriting the disorder. The amniocentesis indicates a daughter.

- a. Why can a genetic test performed on one cell of an 8-celled embryo, the developing placenta, or shed from a fetus predict the future health of the individual?
- b. At the time of preimplantation genetic diagnosis, is the embryo a cleavage embryo, an inner cell mass, or a gastrula?

- c. What structures are present in Vivian and Max's fetus that have not yet developed in Anna and Peter's at the time of their prenatal tests?

13. Surgical separation of conjoined twins is more likely to succeed if fewer body parts are shared or attached. This was the case for Maria de Jesus and Maria Teresa, born in Guatemala in 2001 and separated before their first birthday. They were joined at the head, but facing opposite directions, so they could not move much. The surgery took 23 hours! Today they are well. The outcome wasn't good for Landan and Laleh Bijani, 29-year-old Iranian conjoined twins who could no longer stand being joined along their heads, with their brains fused. They died shortly after 50 hours of surgery in 2003.

If you had conjoined twins, what would you do? Would you attempt surgical separation?

14. Human embryonic stem cells can be derived and cultured from an 8-celled cleavage embryo and from a cell of an inner cell mass. Explain the difference between these stages of human prenatal development.
15. Victor, a 34-year-old artist, was killed in a car accident. He and his wife Emma hadn't started a family yet, but planned to soon. The morning after the accident, Emma asked if some of her husband's sperm could be collected and frozen, for her to use to have a child. Do you think that this “post-mortem sperm retrieval” should be done? See the chapter-opening case study for chapter 21 for further information.

# A Second Look

1. How does ovulation in a woman taking hormones to donate oocytes differ from normal ovulation?
2. Oocyte donation has been done for more than thirty years to help infertile couples. Today oocytes are also sought to derive human embryonic stem cells for research. Several arguments have been given to

oppose paying women to donate oocytes for deriving hES cells:

- Paying would unduly encourage poor women to face risks associated with oocyte donation.
- Paying “commodifies” the act of giving, turning an oocyte into an object.

- Women should want to donate oocytes for altruistic reasons rather than to earn money.
- a. Choose one of these reasons and argue the opposing side—that is, that the payment is justified.



- b. Why might ethical concerns arise for donating oocytes for hES cell research, but not for infertility?
  - c. Under what circumstances do you think it would be ethical for Vanessa's oocytes to be used in hES research?
3. A baby conceived using the father's sperm to fertilize a donor oocyte is born with

a birth defect caused by a drug that the man's wife took while pregnant. The couple wishes to sue the oocyte donor for having provided damaged material. Are they justified? Cite a reason for your answer.

Learn to apply the skills of a genetic counselor with this additional case found in the *Case Workbook in Human Genetics*:

Embryos and "former embryos" in research



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.



# Single-Gene Inheritance

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  - Mendel's Experiments
  - Terms and Tools to Follow Segregating Genes
- 4.2 **Single-Gene Inheritance in Humans**
  - Modes of Inheritance
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- 4.3 **Following the Inheritance of Two Genes—Independent Assortment**
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## CYSTIC FIBROSIS, THEN AND NOW

What do pea plant experiments have to do with human health? For sportswriter Frank Deford and his wife, Carol, patterns of inheritance that the “father of genetics,” Gregor Mendel, demonstrated in peas affected their family with the birth of daughter Alex in 1972. She had digestive difficulties and severe infections before dying of cystic fibrosis at age 8.

Frank Deford wrote about his feelings at the time of the diagnosis in a book, *Alex, the Life of a Child*:

I went to the encyclopedia and read about this cystic fibrosis. To me, at that point, it was one of those vague diseases you hear about now and then. . . . One out of every 20 whites carries the defective gene, as I do, as Carol does, as perhaps 10 million other Americans do. . . . If our second-born had not been cursed with cystic fibrosis, then we probably never would have had another child, and our bad genes would merely have been passed on, blissfully unknown to us.

Deford described recessive inheritance: skipped generations for a trait.

A child born with CF in 1972 was not expected to live much beyond age five. Today, many people with CF live well into adulthood, thanks to:

- Better antibiotics targeted to the pathogens that attack CF-ravaged lungs.
- Improved digestive enzyme supplements.
- New medical devices such as a vibrating vest that shatters mucus in the lungs.

Although severe CF may still be lethal at a young age, many children born today with the disease have more therapeutic options—and often many more years—than children with CF born in 1972.



Treating cystic fibrosis. In cystic fibrosis, the thick, sticky mucus that clogs airways must be coughed up at least twice every day.





**Figure 4.1 Inherited similarities.**

Facial similarities are not always as obvious as those between rock star Steven Tyler of Aerosmith and his actress daughter, Liv. Liv's son Milo also inherited her family's famous facial features.

Inherited similarities can be startling. When Aerosmith singer Steven Tyler first met his daughter, Liv, when she was nine years old, he knew with one glance that she was his child. He burst into tears, so compelling was the resemblance. Father and daughter have strikingly similar facial features (figure 4.1).

## 4.1 Following the Inheritance of One Gene—Segregation

Noting resemblances among blood relatives is one way to recognize heredity. A specific disorder not due to infection that is present in more than one family member is another sign of inheritance. Yet another way to analyze heredity is to identify specific DNA sequences, decipher the proteins that they encode, and discover the functions of the proteins in the body.

The beginnings of the field of genetics bridged these macroscopic and microscopic views of heredity. Gregor Mendel used a series of clever breeding experiments in pea plants to describe units of inheritance that pass traits from generation to generation. He called these units “elementen.” He could not see them, but he inferred their existence from the appearances of his plants. Although Mendel knew nothing of DNA, or even cells or chromosomes, his “laws” of

inheritance have not only stood the test of time, but explain trait transmission in any diploid species—as the problems at the end of the chapter attest.

### Mendel the Man

Mendel spent his early childhood in a small village in what is now the Czech Republic, near the Polish border. His father was a farmer, and his mother was the daughter of a gardener, so Mendel learned early how to tend fruit trees. At age 10 he left home to attend a special school for bright students, supporting himself by tutoring. After a few years at a preparatory school, Mendel became a priest at the Augustinian monastery of St. Thomas in Brnő. At this atypical monastery, the priests were also teachers, and they did research in natural science. From them, Mendel learned how to artificially pollinate crop plants to control their breeding.

Mendel wanted to teach natural history, but had difficulty passing the necessary exams due to test anxiety. At age 29, he was such an effective substitute teacher that he was sent to earn a college degree. At the University of Vienna, courses in the sciences and statistics fueled his interest in plant breeding and got him thinking about experiments to address a question that had confounded other plant breeders—why did certain traits disappear in one generation, yet reappear in the next? To solve this puzzle, Mendel bred hybrids and applied the statistics he had learned in college.

From 1857 to 1863, Mendel crossed and cataloged traits in 24,034 plants, through several generations. He deduced that consistent ratios of traits in the offspring indicated that the plants transmitted distinct units, or “elementen.” He derived two hypotheses to explain how inherited traits are transmitted. Mendel described his work to the Brnő Medical Society in 1865 and published it in the organization's journal the next year. The remarkably clear paper discusses plant hybridization, the reappearance of traits in the third generation, and the joys of working with peas, plus data.

It took years for Mendel's findings to be recognized. Shortly after his treatise was published in English in 1901, three

botanists (Hugo DeVries, Karl Franz Joseph Erich Correns, and Seysenegg Tschermak) independently rediscovered the laws of inheritance. Once they read Mendel's paper, they credited him. Mendel came to be regarded as the “father of genetics.”















In the twentieth century, researchers discovered the molecular basis of some of the traits that Mendel studied. The “short” and “tall” plants reflected the expression of a gene that enables a plant to produce the hormone gibberellin, which elongates the stem. One tiny change to the DNA, and a short plant results. Likewise, “round” and “wrinkled” peas arise from the *R* gene, whose encoded protein connects sugars into branching polysaccharide molecules. Seeds with a mutant gene cannot attach the sugars. As a result, water exits the cells, and the peas wrinkle.

### Mendel's Experiments

Peas are ideal for probing heredity because they are easy to grow, develop quickly, and have many traits that take one of two easily distinguishable forms. **Figure 4.2** illustrates the seven traits that Mendel followed through several pea generations. When analyzing genetic crosses, the first generation is the parental generation, or  $P_1$ ; the second generation is the first filial generation, or  $F_1$ ; the next generation is the second filial generation, or  $F_2$ , and so on.

Mendel's first experiments dealt with single traits with two expressions, such as “short” and “tall.” He set up all combinations of possible artificial pollinations, manipulating fertilizations to cross tall with tall, short with short, and tall with short plants. This last combination, plants with one trait variant crossed to plants with the alternate, produces hybrids, which are offspring that inherit a different gene variant from each parent.

Mendel noted that short plants crossed to other short plants were “true-breeding,” always producing short plants. The crosses of tall plants to each other were more confusing. Some tall plants were true-breeding, but others crossed with each other yielded short plants in about one-quarter of the next generation. It appeared as if in some tall plants, tallness could mask

	Seed form	Seed color	Pod form	Pod color	Flower position	Seed coat color	Stem length
Dominant							
	Round ( <i>R</i> )	Yellow ( <i>Y</i> )	Inflated ( <i>V</i> )	Green ( <i>G</i> )	Axial ( <i>F</i> ) along stem	Gray or gray-brown ( <i>A</i> )	Tall ( <i>T</i> )
Recessive							
	Wrinkled ( <i>r</i> )	Green ( <i>y</i> )	Restricted ( <i>v</i> )	Yellow ( <i>g</i> )	Terminal ( <i>f</i> ) on top	White ( <i>a</i> )	Short ( <i>t</i> )

**Figure 4.2 Traits Mendel studied.** Gregor Mendel studied the transmission of seven traits in the pea plant. Each trait has two easily distinguished expressions, or phenotypes.

shortness. One trait that masks another is said to be **dominant**; the masked trait is **recessive**.

Mendel conducted up to 70 hybrid crosses for each of the seven traits. Because one trait is followed and the parents are hybrids, this is called a **monohybrid cross**.

When Mendel allowed the non-true-breeding tall plants—monohybrids—to self-fertilize, the progeny were in the ratio of one-quarter short to three-quarters tall plants (**figure 4.3**). In further crosses, he found that two-thirds of the tall plants from the monohybrid  $F_1$  cross were non-true-breeding, and the remaining third were true-breeding.

In these experiments, Mendel confirmed that hybrids hide one expression of a trait—short, in this case—which reappears when hybrids are self-crossed. He tried to explain how this happened: Gametes distribute “elementen” because these cells physically link generations. Paired sets of elementen separate as gametes form. When gametes join at fertilization, the elementen combine anew. Mendel reasoned that each elementen was packaged in a separate gamete. If opposite-sex gametes

combine at random, he could mathematically explain the different ratios of traits produced from his pea plant crosses. Mendel’s idea that elementen separate in the gametes would later be called the **law of segregation**. Frustrated at the lack of recognition he received as a scientist, Mendel eventually turned his energies to monastery administration.

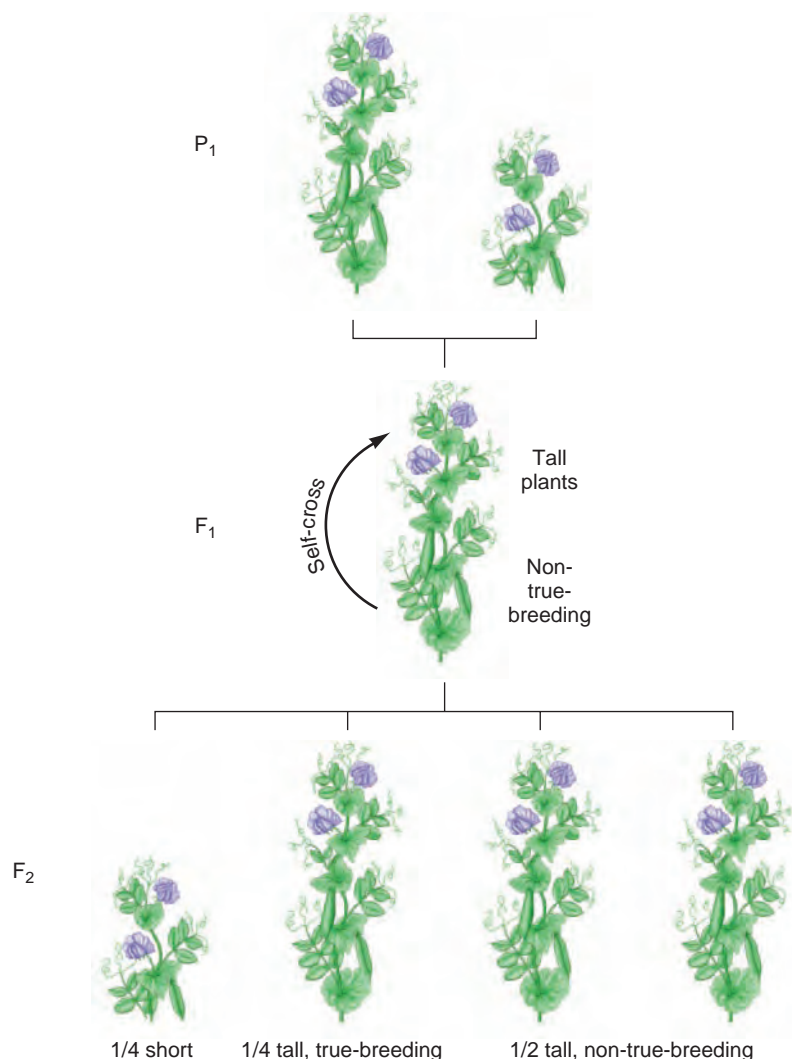
When Mendel’s ratios were demonstrated in several species in the early 1900s, just when chromosomes were being described for the first time, it became apparent that elementen and chromosomes had much in common. Both paired elementen and pairs of chromosomes separate at each generation and are transmitted—one from each parent—to offspring. Both elementen and chromosomes are inherited in random combinations. Therefore, chromosomes provided a physical mechanism for Mendel’s hypotheses. In 1909, English embryologist William Bateson renamed Mendel’s elementen *genes* (Greek for “give birth to”). It wasn’t until the 1940s, however, that scientists began investigating the gene’s chemical basis. We pick up the historical trail at this point in chapter 9.

## Terms and Tools to Follow Segregating Genes

The law of segregation reflects the actions of chromosomes and genes during meiosis. Because a gene is a long sequence of DNA, it can vary in many ways. An individual with two identical alleles for a gene is **homozygous** for that gene. An individual with two different alleles is **heterozygous**—what Mendel called “non-true-breeding” or “hybrid.”

When considering a gene with two alleles, it is common to symbolize the dominant one with a capital letter and the recessive with the corresponding small letter. If both alleles are recessive, the individual is homozygous recessive. Two small letters, such as *tt* for short plants, symbolize this. An individual with two dominant alleles is homozygous dominant. Two capital letters, such as *TT* for tall pea plants, represent this. Another possible allele combination is one dominant and one recessive allele—*Tt* for non-true-breeding tall pea plants, or heterozygotes.

An organism’s appearance does not always reveal its alleles. Both a *TT* and a *Tt* pea plant are tall, but *TT* is a homozygote and *Tt* a heterozygote. The **genotype**



**Figure 4.3 A monohybrid cross.** When Mendel crossed true-breeding tall plants with short plants, the next generation plants were all tall. When he self-crossed the F<sub>1</sub> plants, one-quarter of the plants in the next generation, the F<sub>2</sub>, were short, and three-quarters were tall. Of the tall plants in the F<sub>2</sub>, one-third were true-breeding, and the other two-thirds were not true-breeding. He could tell this by conducting further crosses of the tall plants to short plants, to see which bred true.

describes the organism's alleles, and the **phenotype** describes the outward expression of an allele combination. A **wild type** phenotype is the most common expression of a particular allele combination in a population. The wild type allele may be recessive or dominant. A **mutant** phenotype is a variant of a gene's expression that arises when the gene undergoes a change, or **mutation**.

Although he didn't realize it, Mendel was observing signs of the events of meiosis. When a gamete is produced, the two copies of a particular gene separate along with the homologs that carry them. In a plant of genotype *Tt*, for example, gametes carrying either *T* or *t* form in equal numbers during anaphase I. When gametes meet at the next generation, they combine at random. That is, a *t*-bearing oocyte is neither more nor less attractive to a sperm than is a *T*-bearing oocyte. These two factors—equal allele distribution into gametes and random combinations of gametes—underlie Mendel's law of segregation (**figure 4.4**).

When Mendel crossed short plants (*tt*) with true-breeding tall plants (*TT*), the seeds grew into F<sub>1</sub> plants that were all tall (genotype *Tt*). Next, he self-crossed the F<sub>1</sub> plants. The progeny were *TT*, *tt*, and *Tt*. A *TT* individual resulted when a *T* sperm fertilized a *T* oocyte; a *tt* plant resulted when a *t* oocyte met a *t* sperm; and a *Tt* individual resulted when either a *t* sperm fertilized a *T* oocyte, or a *T* sperm fertilized a *t* oocyte.

Because two of the four possible gamete combinations produce a heterozygote, and each of the others produces a homozygote, the genotypic ratio expected of a monohybrid cross is 1 *TT*: 2*Tt*: 1*tt*. The corresponding phenotypic ratio is three tall plants to one short plant, a 3:1 ratio. Mendel saw these results for all seven traits that he studied (**table 4.1**). A diagram called a **Punnett square** shows these ratios (**figure 4.5**). A Punnett square represents how particular genes in gametes come together, assuming they are carried on different chromosomes. Experimental crosses yield numbers of offspring that approximate these ratios.

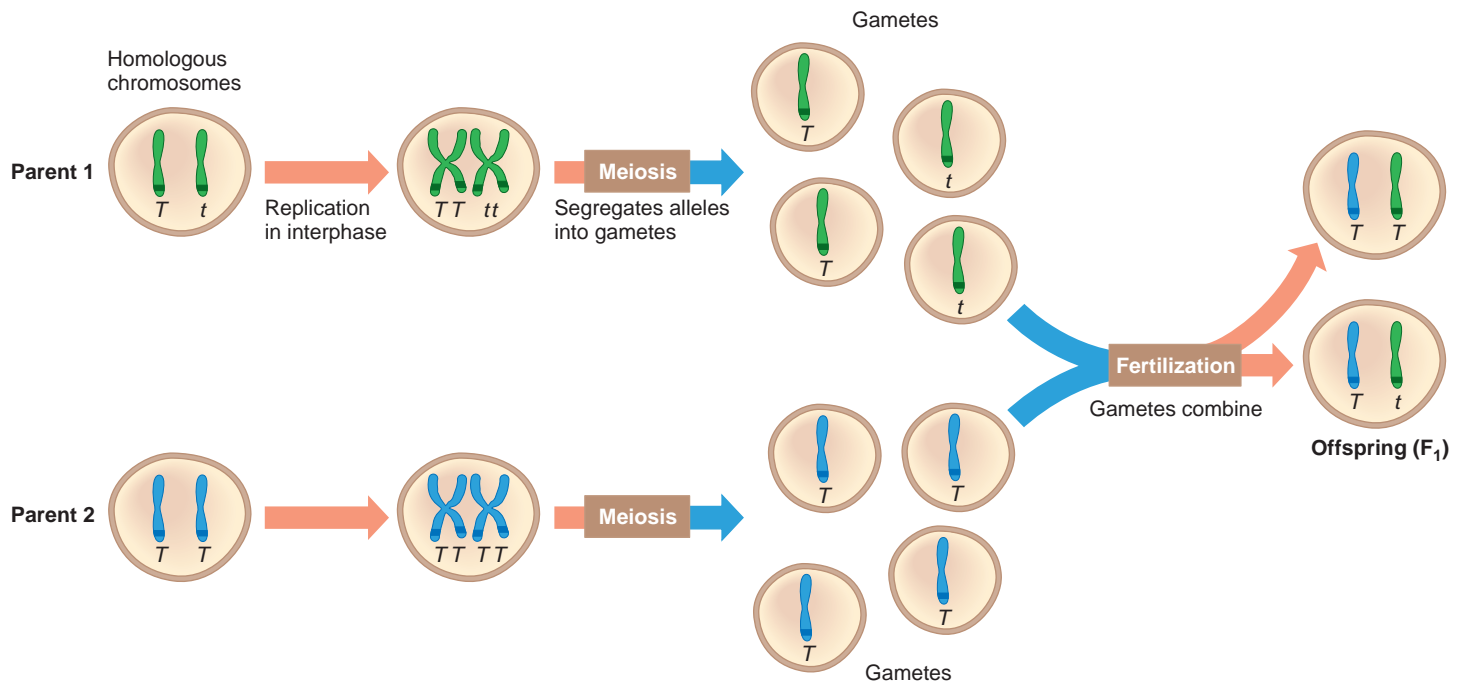
Mendel distinguished the two genotypes resulting in tall progeny—*TT* from *Tt*—with additional crosses (**figure 4.6**). He bred tall plants of unknown genotype with short (*tt*) plants. If a tall plant crossed with a *tt* plant produced both tall and short progeny,

**Table 4.1**

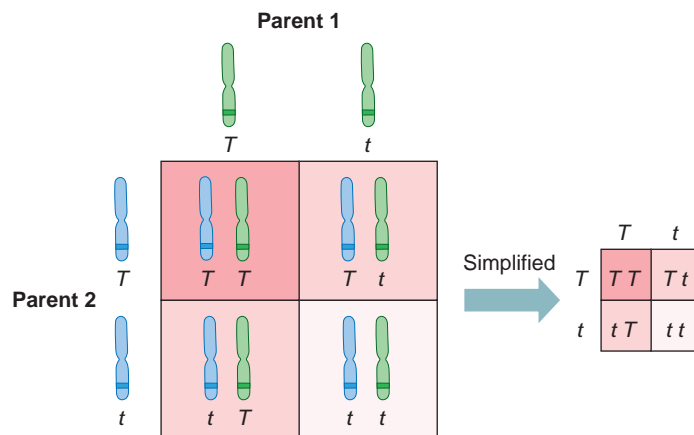
### Mendel's Law of Segregation

Experiment	Total	Dominant	Recessive	F <sub>2</sub> Phenotypic Ratios
1. Seed form	7,324	5,474	1,850	2.96:1
2. Seed color	8,023	6,022	2,001	3.01:1
3. Seed coat color	929	705	224	3.15:1
4. Pod form	1,181	882	299	2.95:1
5. Pod color	580	428	152	2.82:1
6. Flower position	858	651	207	3.14:1
7. Stem length	1,064	787	277	<u>2.84:1</u>
				Average = 2.98:1





**Figure 4.4 Mendel's first law—gene segregation.** During meiosis, homologous pairs of chromosomes (and the genes that compose them) separate from one another and are packaged into separate gametes. At fertilization, gametes combine at random to form the individuals of a new generation. Green and blue denote different parental origins of the chromosomes. In this example, offspring of genotypes  $TT$  and  $Tt$  are generated.

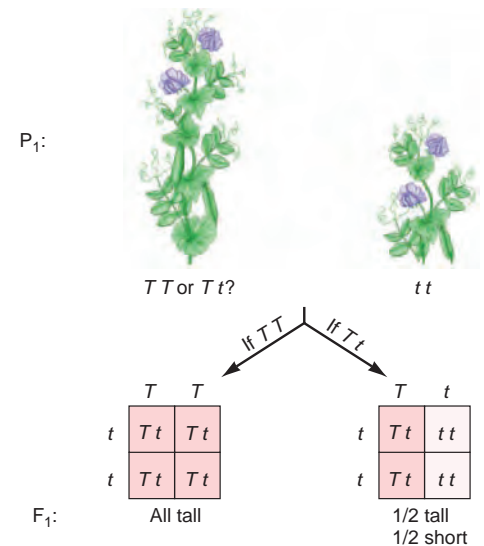


**Figure 4.5 A Punnett square.** A Punnett square illustrates how alleles combine in offspring. The different types of gametes of one parent are listed along the top of the square, with those of the other parent listed on the left-hand side. Each compartment displays the genotype that results when gametes that correspond to that compartment join. This Punnett square describes a monohybrid cross of two tall pea plants. Among the progeny, tall plants outnumber short plants 3:1. Can you determine the genotypic ratio? Punnett squares usually indicate only the alleles, as shown at the right.

Mendel knew it was genotype  $Tt$ ; if it produced only tall plants, he knew it must be  $TT$ .

Crossing an individual of unknown genotype with a homozygous recessive

individual is called a test cross. It is based on the logic that the homozygous recessive is the only genotype that can be identified by its phenotype—that is, a short plant



**Figure 4.6 Test cross.** Breeding a tall pea plant with homozygous recessive short plants reveals whether the tall plant is true-breeding ( $TT$ ) or non-true-breeding ( $Tt$ ).

## Key Concepts

1. Mendel deduced that "elementen" for height segregate during meiosis, then combine at random with those from the opposite gamete at fertilization.
2. A homozygote has two identical alleles, and a heterozygote has two different alleles. The allele expressed in a heterozygote is dominant; the allele not expressed is recessive.
3. A monohybrid cross yields a genotypic ratio of 1:2:1 and a phenotypic ratio of 3:1.
4. Punnett squares display expected genotypic and phenotypic ratios among progeny.
5. A test cross uses a homozygous recessive individual to reveal an unknown genotype.

## 4.2 Single-Gene Inheritance in Humans

Mendel's first law addresses traits determined by single genes. Inheritance of single genes is also called Mendelian, or monofactorial inheritance.

Since the sequencing of the human genome, however, and the identification of many genes, it is becoming clear that nearly all disorders and traits once considered to be caused by single genes are actually influenced by environmental factors and usually by the actions of other genes, too. For example, although CF is a single-gene disorder, lung infection can be severe and prolonged because a protein released as part of the immune response, interleukin-23, is produced in some patients long after the infection has been squelched.

Even the most familiar single-gene disorders, such as sickle cell disease and Duchenne muscular dystrophy, are rare compared to infectious diseases, cancer, and multifactorial disorders. Most single-gene conditions affect 1 in 10,000 or fewer individuals. **Table 4.2** lists some single-gene disorders, and **Reading 4.1** considers some interesting traits described in *Online Mendelian Inheritance in Man*.

### Modes of Inheritance

**Modes of inheritance** are rules that explain the common patterns that inherited characteristics follow as they are passed through families. Knowing the mode of inheritance makes it possible to calculate the probability that a particular couple will have a child who inherits a particular condition.

**Table 4.2**

### Some Single-Gene Disorders in Humans

Disorder	OMIM	Symptoms
<b>Autosomal Recessive</b>		
Ataxia telangiectasis	208900	Facial rash, poor muscular coordination, involuntary eye movements, high risk for cancer, and respiratory infections
Batten disease	204500	Visual loss, developmental delay, seizures
Cystic fibrosis	219700	Lung infections and congestion, poor fat digestion, male infertility, poor weight gain, salty sweat
Familial hypertrophic cardiomyopathy	192600	Overgrowth of heart muscle, causing sudden death in young adults
Gaucher disease	230800	Swollen liver and spleen, anemia, internal bleeding, poor balance
Hemochromatosis	235200	Iron retention; high risk of infection, liver damage, excess skin pigmentation, heart and pancreas damage
Maple syrup urine disease	248600	Lethargy, vomiting, irritability, mental retardation, coma, and death in infancy
Phenylketonuria	261600	Mental retardation, fair skin
Sickle cell disease	603903	Joint pain, spleen damage, high risk of infection
Tay-Sachs disease	272800	Nervous system degeneration
<b>Autosomal Dominant</b>		
Achondroplasia	100800	Dwarfism with short limbs, normal-size head and trunk
Familial hypercholesterolemia	144010	Very high serum cholesterol, heart disease
Huntington disease	143100	Progressive uncontrollable movements and personality changes, beginning in middle age
Lactose intolerance	150220	Inability to digest lactose, causing cramps after ingestion
Marfan syndrome	154700	Long limbs, sunken chest, lens dislocation, spindly fingers, weakened aorta
Myotonic dystrophy	160900	Progressive muscle wasting
Neurofibromatosis (1)	162200	Brown skin marks, benign tumors beneath skin
Polycystic kidney disease	173900	Cysts in kidneys, bloody urine, high blood pressure, abdominal pain
Polydactyly	174200	Extra fingers and/or toes
Porphyria variegata	176200	Red urine, fever, abdominal pain, headache, coma, death



## Reading 4.1

### It's All in the Genes

Do you have uncombable hair, misshapen toes or teeth, or a pigmented tongue tip? Are you unable to smell a squashed skunk, or do you sneeze repeatedly in bright sunlight? Do you lack teeth, eyebrows, eyelashes, nasal bones, thumbnails, or fingerprints? If so, your unusual trait may be one of thousands described in OMIM. Entering a disease name retrieves family histories, clinical descriptions, mode of inheritance, and molecular information. Amidst the medical terminology and genetic jargon are the stories behind some fascinating traits.

Genes control whether hair is blond, brown, or black, has red highlights, and is straight, curly, or kinky. Widow's peaks, cowlicks, a whorl in the eyebrow, and white forelocks run in families; so do hairs with triangular cross-sections. Some people have multicolored hairs, like cats; others have hair in odd places, such as on the elbows, nose tip, knuckles, palms, or soles. Teeth can be missing or extra, protuberant or fused, present at birth, shovel-shaped, or "snow-capped." A person can have a grooved tongue, duckbill lips, flared ears, egg-shaped pupils, three rows of eyelashes, spotted nails, or "broad thumbs and great toes." Extra breasts are known in humans and guinea pigs, and one family's claim to genetic fame is a double nail on the littlest toe.

Unusual genetic variants can affect metabolism, producing either disease or harmless, yet noticeable, effects. Members of some families experience "urinary excretion of odoriferous component of asparagus" or "urinary excretion of beet pigment," producing a strange odor or dark pink urine after consuming the offending vegetable. In blue diaper syndrome, an infant's urine turns blue on contact with air, thanks to an inherited inability to break down an amino acid.

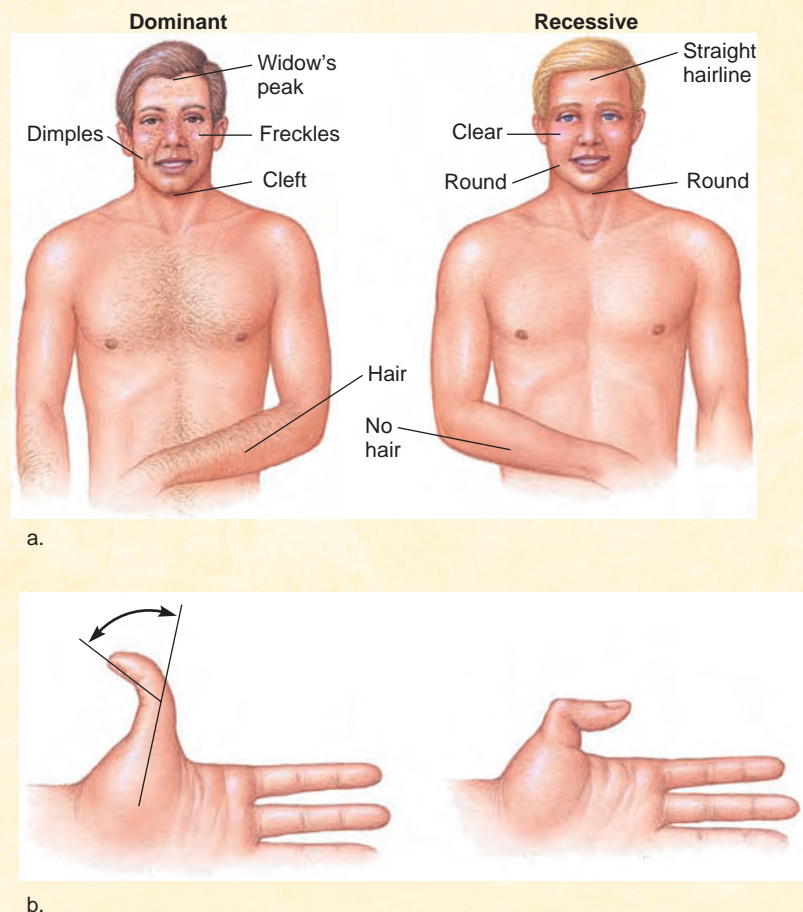
One bizarre inherited illness is the Jumping Frenchmen of Maine syndrome (OMIM 244100). This exaggerated startle

reflex was first noted among French-Canadian lumberjacks from the Moosehead Lake area of Maine, whose ancestors were from the Beauce region of Quebec. Physicians first reported the condition at a medical conference in 1878. Geneticists videotaped the startle response in 1980, and the condition continues to appear in genetics journals. OMIM offers a most vivid description:

**If given a short, sudden, quick command, the affected person would respond with**

**the appropriate action, often echoing the words of command. . . . For example, if one of them was abruptly asked to strike another, he would do so without hesitation, even if it was his mother and he had an ax in his hand.**

The Jumping Frenchmen of Maine syndrome may be an extreme variant of the more common Tourette syndrome, which causes tics and other uncontrollable movements. **Figure 1** illustrates some other genetic variants.



**Figure 1 Inheritance of some common traits.** (a) Freckles, dimples, hairy arms, widow's peak, and a cleft chin are examples of dominant traits. (b) The ability to bend the thumb backward or forward is inherited.



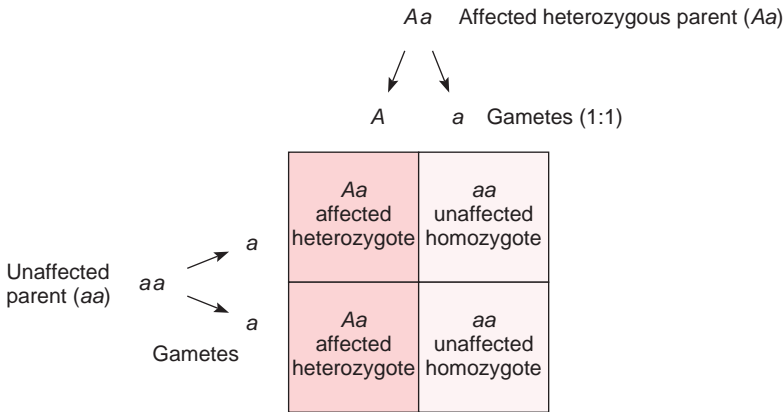
For example, after a child is diagnosed with cystic fibrosis, the parents learn that each of their future children faces a 1 in 4 chance of inheriting the illness.

Mendel studied traits carried on autosomes (non-sex chromosomes). The way a trait is passed depends on whether it is determined by a gene on an autosome or on a sex chromosome, and whether the particular allele is recessive or dominant. **Autosomal dominant** and **autosomal recessive** are the two modes of inheritance directly derived from Mendel’s laws.

### Autosomal Dominant Inheritance

In autosomal dominant inheritance, a trait can appear in either sex because an autosome carries the gene. If a child has the trait, at least one parent also has it. That is, autosomal dominant traits do not skip generations. If no offspring inherit the trait in one generation, its transmission stops because the offspring can pass on only the recessive form of the gene. **Figure 4.7** uses a Punnett square to predict the genotypes and phenotypes of offspring of a mother who has an autosomal dominant trait and a father who does not.

A young man, James Poush, discovered an autosomal dominant trait in his family while in high school and published the first full report on distal symphalangism. James and certain relatives had stiff fingers and toes with tiny nails. When he studied genetics, he realized this might be a Mendelian



**Figure 4.7 Autosomal dominant inheritance.** When one parent has an autosomal dominant condition and the other does not, each offspring has a 50 percent probability of inheriting the mutant allele and the condition. The affected parent is Aa here, and not AA, because for many dominant disorders, the homozygous dominant (AA) phenotype is either lethal or very rare because both parents of the person with the AA genotype would have to have the disorder.

Table 4.3
Criteria for an Autosomal Dominant Trait
1. Males and females can be affected. Male-to-male transmission can occur.
2. Males and females transmit the trait with equal frequency.
3. Successive generations are affected.
4. Transmission stops after a generation in which no one is affected.

trait. James identified 27 affected individuals among 156 relatives, and concluded that the trait is autosomal dominant. Of 63 relatives with an affected parent, 27 (43 percent) were affected—close to the 50 percent expected for autosomal dominant inheritance (**table 4.3**). **Bioethics:** Choices for the Future (page 77) considers the dilemma of detecting autosomal dominant mutant genes before symptoms arise for an untreatable illness.

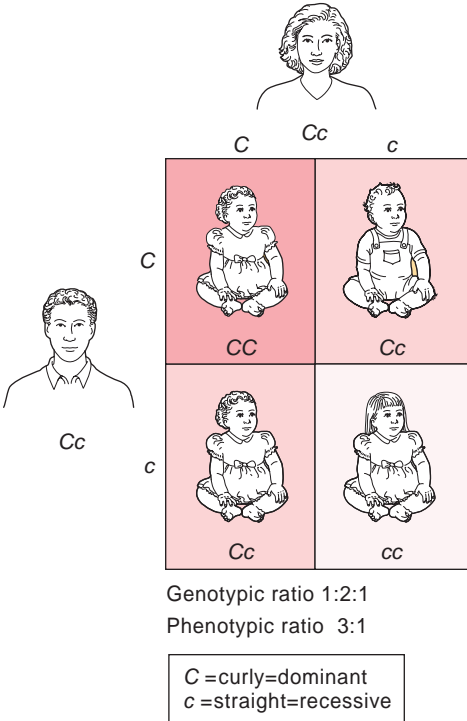
### Autosomal Recessive Inheritance

An autosomal recessive trait can appear in either sex. Affected individuals have a homozygous recessive genotype, whereas in heterozygotes—also called “carriers”—the wild type allele masks expression of the mutant allele. Alex Deford, the little girl with CF described in the chapter opener,

inherited a mutant allele from each of her carrier parents. They were unaffected because they each also had a dominant allele that encodes enough functional protein for health. **Figure 4.8** depicts the autosomal recessive inheritance pattern of a more benign trait, curly hair.

Mendel’s first law can be used to calculate the probability that an individual will have either of two phenotypes. The probabilities of each possible genotype are added. For example, the chance that a child whose parents are both carriers of cystic fibrosis will *not* have the condition is the sum of the probability that she has inherited two normal alleles (1/4) plus the chance that she herself is a heterozygote (1/2), or 3/4. Note that this also equals 1 minus the probability that she is homozygous recessive and has the condition.

The ratios that Mendel’s first law predicts for autosomal recessive inheritance apply to each offspring anew. Misunderstanding this concept leads to a common problem in genetic counseling. Many people conclude that if they have already had a child



**Figure 4.8 Autosomal recessive inheritance.** A 1:2:1 genotypic ratio results from a monohybrid cross, whether in peas or people. Curly hair (C) is dominant to straight hair (c). This pedigree depicts a monohybrid cross for curly hair.

affected by an autosomal recessive illness, then their next three children are guaranteed to escape it. This isn't true. Each child faces the same 25 percent risk of inheriting the condition.

Most autosomal recessive conditions occur unexpectedly in families. However, blood relatives who have children together have a much higher risk of having a child with an autosomal recessive condition, because they may carry the same alleles inherited from an ancestor that they have in common, such as a grandparent. Marriage between relatives introduces **consanguinity**, which means "shared blood"—a figurative description, since genes are not passed in blood.

Blood relatives can trace their families back to a common ancestor. An unrelated man and woman have eight different grandparents, but first cousins have only six, because they share one pair through their parents, who are siblings (see figure 4.14c). That is, the probability of two relatives inheriting the same disease-causing recessive allele is greater than that of two

unrelated people having the same allele by chance. (Chapter 7 discusses different types of cousins.)

The nature of the phenotype is important when evaluating the transmission of single-gene traits. For example, each adult sibling of a person who is a known carrier of Tay-Sachs disease has a two-thirds chance of being a carrier. The probability is two-thirds, and not one-half, because there are only two genotypes possible for an adult—homozygous for the wild type allele or a carrier who inherits the mutant allele from either mother or father. A homozygous recessive individual would not have survived childhood.

Geneticists who study human traits and illnesses can hardly set up crosses as Mendel did, but they can pool information from families whose members have the same trait or illness. Consider a simplified example of 50 couples in whom both partners are carriers of sickle cell disease. If 100 children are born, about 25 of them would be expected to have sickle cell disease. Of the remaining 75, theoretically 50 would be carriers like

**Table 4.4**

### Criteria for an Autosomal Recessive Trait

1. Males and females can be affected.
2. Affected males and females can transmit the gene, unless it causes death before reproductive age.
3. The trait can skip generations.
4. Parents of an affected individual are heterozygous or have the trait.

their parents, and the remaining 25 would have two wild type alleles. **Table 4.4** lists criteria for an autosomal recessive trait.

### Solving a Problem: Segregation

Using Mendel's laws to predict phenotypes and genotypes requires a careful reading of the problem to identify and organize relevant information. Sometimes common sense is useful, too. The following general

## Bioethics: Choices for the Future

### When Diagnosing a Fetus Also Diagnoses a Parent: Huntington Disease (HD)

When Peter and Martha were 24 and expecting their first child, they learned that Peter's mother, who was adopted, had early signs of HD. Her clumsiness and slurred speech would eventually progress to a near-constant writhing and repetitive, dance-like movements, until she would die, probably of infection, in fifteen to twenty years.

A genetic counselor told the couple that because HD is autosomal dominant, Peter had a 50 percent (1 in 2) chance of having inherited the condition. He was considered "at-risk" until (and if) symptoms began. However, he could take a "predictive" genetic test that would reveal whether he had inherited HD. Peter was glad that he didn't have any siblings to worry about, but he told the counselor, his parents, and Martha that he did not want to know if HD lay in his future. Martha, however, felt differently. She did not

want to have a child who would have HD. Could the fetus be checked for the mutation? Then, if the disease had been inherited, the couple could end the pregnancy.

The problem was that if the fetus had the mutation, then so did Peter, and he didn't want to know. Another issue was that physicians discourage testing for genetic conditions in anyone under 18 when symptoms would not begin until adulthood. Delaying testing would give the affected individual the choice. Whose rights should prevail in this case? Peter's, Martha's, or their future child's?

To help them decide, the couple researched how others had handled the dilemmas that predictive testing for an untreatable, adult-onset illness raise. They read that only about 10 percent of people offered the test for HD take it, and those

that do can handle the results well. After much soul-searching, Martha chose to respect Peter's wishes. So far, both Peter and their son are healthy.

Postscript: Although Peter still does not wish to know whether he will get HD, he is participating in an "observational" medical study. He and 1,000 other at-risk individuals have given a blood sample to researchers at the University of Rochester in New York, and will be followed medically every 9 months for 10 years. The HD genotype will be determined from the initial blood sample, but the participants will not be told of their status, per their wishes. The investigators, however, will know the information, and use the regular medical exams to identify the very earliest signs and symptoms of the disease—which might suggest treatments.



steps can help to solve a problem that addresses Mendel's first law, which describes the inheritance of a single-gene trait.

1. List all possible genotypes and phenotypes for the trait.
2. Determine the genotypes of the individuals in the first ( $P_1$ ) generation. This may require deductive reasoning based on information about those individuals' parents.
3. After deducing genotypes, derive the possible alleles in gametes produced by each individual in the cross.
4. Unite these gametes in all combinations, using a Punnett square if necessary, to reveal all possible genotypes. Calculate ratios for the first generation of offspring ( $F_1$ ).
5. To extend predictions to the second offspring ( $F_2$ ) generation, use the genotypes of the specified  $F_1$  individuals and repeat steps 3 and 4.

As an example, consider curly hair, depicted in figure 4.8. If  $C$  is the dominant allele, conferring curliness, and  $c$  is the recessive allele, then both  $CC$  and  $Cc$  genotypes result in curly hair. A person with  $cc$  genotype has the straight hair phenotype.

Wendy has beautiful curls, and her husband Rick has straight hair. Wendy's father is bald, but once had curly hair, and her mother has stick-straight hair. What is the probability that Wendy and Rick's child will have straight hair? Steps 1 through 5 solve the problem:

1. State possible genotypes:  $CC$ ,  $Cc$  = curly  $cc$  = straight
  2. Determine genotypes: Rick must be  $cc$ , because his hair is straight. Wendy must be  $Cc$ , because her mother has straight hair and therefore gave her a  $c$  allele.
  3. Determine gametes: Rick's sperm carry only  $c$ . Half of Wendy's oocytes carry  $C$ , and half carry  $c$ .
  4. Unite the gametes:
- |      |     | Wendy |      |
|------|-----|-------|------|
|      |     | $C$   | $c$  |
| Rick | $c$ | $Cc$  | $cc$ |
|      | $c$ | $Cc$  | $cc$ |
5. Conclusion: Each child of Wendy and Rick has a 50 percent chance of having curly hair ( $Cc$ ) and a 50 percent chance of having straight hair ( $cc$ ).

## On the Meaning of Dominance and Recessiveness

Determining whether an allele is dominant or recessive is critical in medical genetics because it helps predict which individuals are at high risk of inheriting a particular condition (phenotype). Dominance and recessiveness arise from the genotype, and reflect the characteristics or abundance of a protein.

Mendel based his definitions of dominance and recessiveness on what he could see—one allele masking the other. Today we can often add a cellular or molecular explanation. Consider inborn errors of metabolism caused by absent enzymes. These disorders tend to be recessive. Although cells of a carrier make half the normal amount of the enzyme, this is usually sufficient to maintain health. The one normal allele, therefore, compensates for the mutant one, to which it is dominant. The situation is similar in pea plants. Short stem length results from deficiency of an enzyme that activates a growth hormone, but the  $Tt$  plants produce enough hormone to attain the same height as  $TT$  plants.

A recessive trait is sometimes said to demonstrate a "loss of function" because the recessive allele usually causes the loss of normal protein production and function, so there is too little of a particular protein. In contrast, some dominantly inherited disorders result from the action of an abnormal protein that interferes with the function of the normal protein. Huntington disease is an example of such a "gain of function" disorder. The dominant mutant allele encodes an abnormally long protein that prevents the normal protein from functioning in certain brain cells. Researchers determined that Huntington disease represents a gain of function because individuals who are missing one copy of the gene do not have the illness. That is, the protein encoded by the mutant HD allele must be abnormal, not absent, to cause the disease.

Recessive disorders tend to be more severe, and produce symptoms at much earlier ages, than dominant disorders. Disease-causing recessive alleles can remain, and even flourish, in populations because heterozygotes carry them without becoming ill and pass them to future generations. In

contrast, if a dominant mutation arises that harms health early in life, people who have the allele are either too ill or do not survive long enough to reproduce. The allele eventually becomes rare in the population unless it is replaced by mutation. Dominant disorders whose symptoms do not appear until adulthood, or that do not drastically disrupt health, tend to remain in a population because they do not affect health until after a person has reproduced. Therefore, the dominant conditions that persist tend to be those that first cause symptoms in middle adulthood—such as Huntington disease.

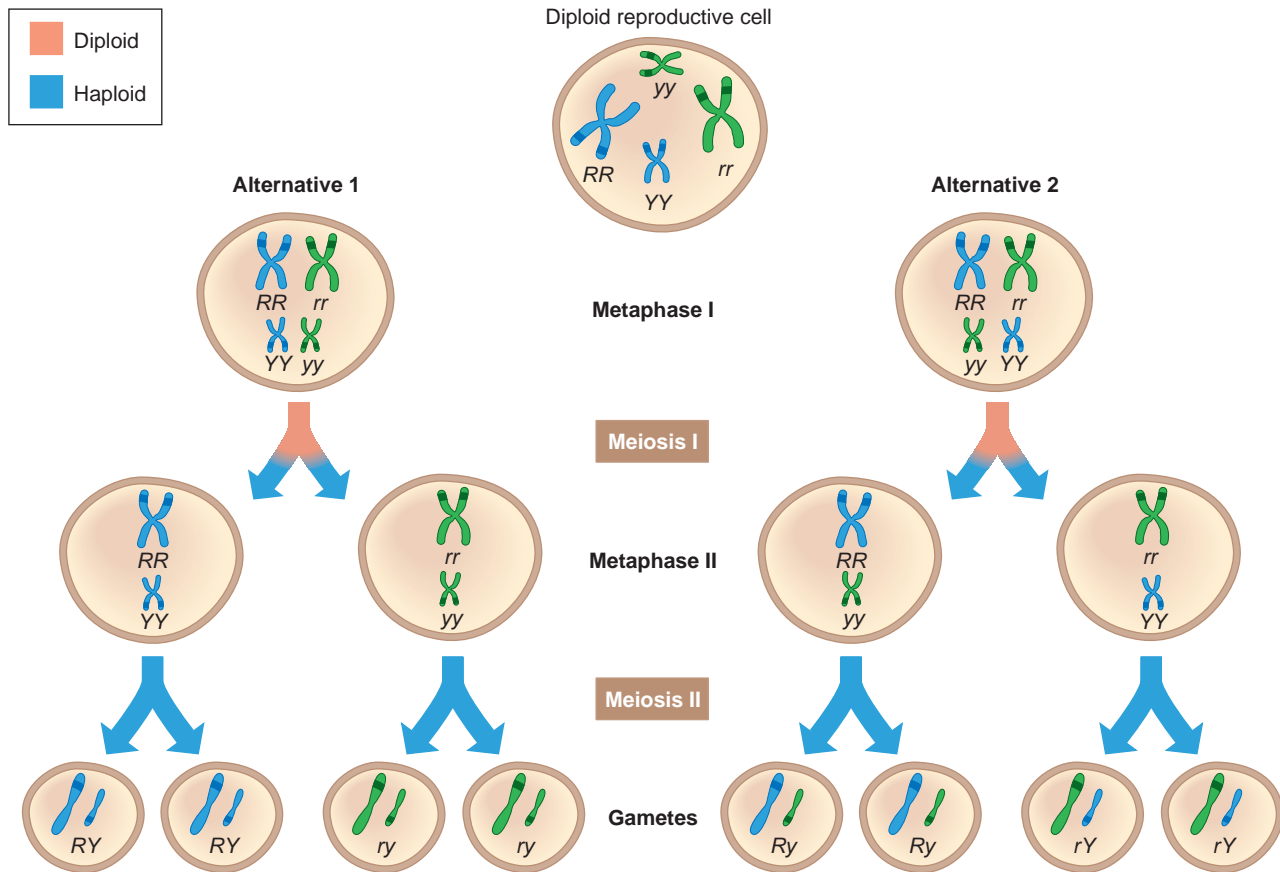
## Key Concepts

1. Modes of inheritance reveal whether a single-gene trait is dominant or recessive and whether the gene that controls it is carried on an autosome or a sex chromosome.
2. Autosomal dominant traits do not skip generations and can affect both sexes; autosomal recessive traits can skip generations and can affect both sexes.
3. Rare autosomal recessive disorders sometimes recur in families when parents are related.
4. Mendel's first law, which can predict the probability that a child will inherit a single-gene trait, applies anew to each child.
5. Genetic problems are solved with logic and by applying Mendel's laws to follow gametes.
6. At the biochemical level, dominance is the ability of a protein encoded by one allele to compensate for a missing or abnormal protein encoded by another allele.

## 4.3 Following the Inheritance of Two Genes—Independent Assortment

The law of segregation follows the inheritance of two alleles for a single gene. In a second set of experiments, Mendel examined the inheritance of two different traits, each attributable to a gene with two different alleles.





**Figure 4.9 Mendel's second law—Independent assortment.** The independent assortment of genes carried on different chromosomes results from the random alignment of chromosome pairs during metaphase of meiosis I. An individual of genotype *RrYy*, for example, manufactures four types of gametes, containing the dominant alleles of both genes (*RY*), the recessive alleles of both genes (*ry*), and a dominant allele of one with a recessive allele of the other (*Ry* or *rY*). The allele combination depends upon which chromosomes are packaged together in a gamete—and this happens at random.

## Mendel's Second Law

The second law, the **law of independent assortment**, states that for two genes on different chromosomes, the inheritance of one does not influence the chance of inheriting the other. The two genes thus “independently assort” because they are packaged into gametes at random (**figure 4.9**). Two genes that are far apart on the same chromosome also appear to independently assort, because so many crossovers occur between them that it is as if they are carried on separate chromosomes (see **figure 3.5**.)

Mendel looked at seed shape, which was either round or wrinkled (determined by the *R* gene), and seed color, which was either yellow or green (determined by the *Y* gene). When he crossed true-breeding plants that had round, yellow seeds to true-breeding plants that had wrinkled, green seeds, all

the progeny had round, yellow seeds. These offspring were double heterozygotes, or dihybrids, of genotype *RrYy*. From their appearance, Mendel deduced that round is dominant to wrinkled, and yellow to green.

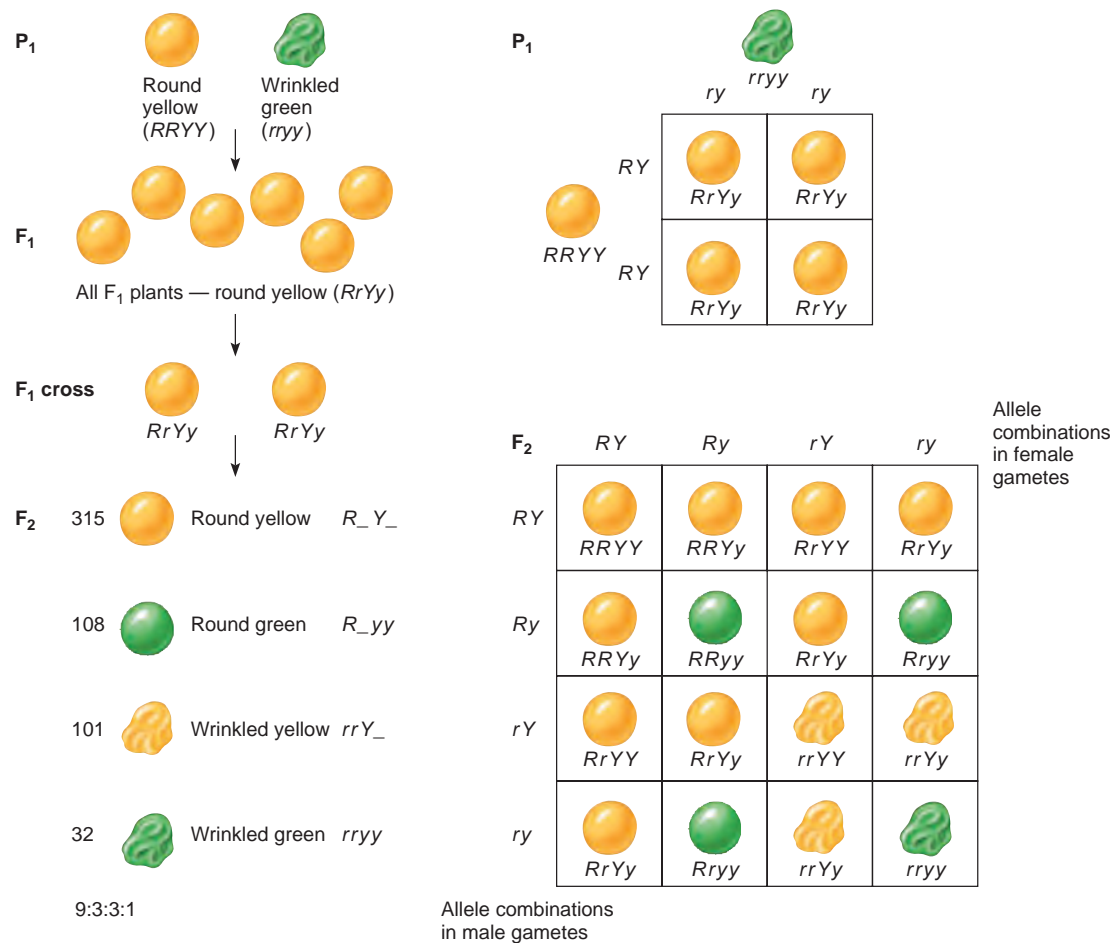
Next, he self-crossed the dihybrid plants in a **dihybrid cross**, so named because two genes and traits are followed. Mendel found four types of seeds in the next, third generation: 315 plants with round, yellow seeds; 108 plants with round, green seeds; 101 plants with wrinkled, yellow seeds; and 32 plants with wrinkled, green seeds. These classes occurred in a ratio of 9:3:3:1.

Mendel then took each plant from the third generation and crossed it to plants with wrinkled, green seeds (genotype *rryy*). These test crosses established whether each plant in the third generation was true-breeding for both genes (genotypes *RRYY* or *rryy*), true-breeding for one gene but

heterozygous for the other (genotypes *RRYy*, *RrYY*, *rrYy*, or *Rryy*), or heterozygous for both genes (genotype *RrYy*). Mendel could explain the 9:3:3:1 proportion of progeny classes only if one gene does not influence transmission of the other. Each parent would produce equal numbers of four different types of gametes: *RY*, *Ry*, *rY*, and *ry*. Note that each of these combinations has one gene for each trait. A Punnett square for this cross shows that the four types of seeds:

1. round, yellow (*RRYY*, *RrYY*, *RRYy*, and *RrYy*)
2. round, green (*RRyy* and *Rryy*)
3. wrinkled, yellow (*rrYY* and *rrYy*) and
4. wrinkled, green (*rryy*)

are present in the ratio 9:3:3:1, just as Mendel found (**figure 4.10**).



**Figure 4.10 Plotting a dihybrid cross.** A Punnett square can represent the random combinations of gametes produced by dihybrid individuals. An underline in a genotype (in the F<sub>2</sub> generation) indicates that either a dominant or a recessive allele is possible. The numbers in the F<sub>2</sub> generation are Mendel's experimental data.

## Solving a Problem: Following More Than One Segregating Gene

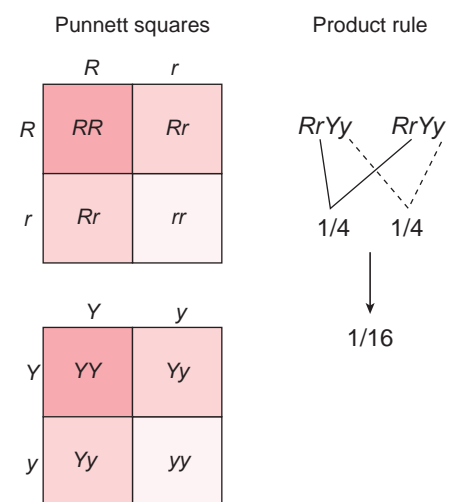
A Punnett square for three genes has 64 boxes; for four genes, 256 boxes. An easier way to predict genotypes and phenotypes in multi-gene crosses is to use the mathematical laws of probability on which Punnett squares are based. Probability predicts the likelihood of an event.

An application of probability theory called the product rule can predict the chance that parents with known genotypes can produce offspring of a particular genotype. The product rule states that the chance that two independent events will both occur equals the product of the chance that either event will occur alone. Consider the probability of obtaining a plant with wrinkled, green peas (genotype *rryy*) from dihybrid (*RrYy*) parents. Do the reasoning for one

gene at a time, then multiply the results (**figure 4.11**).

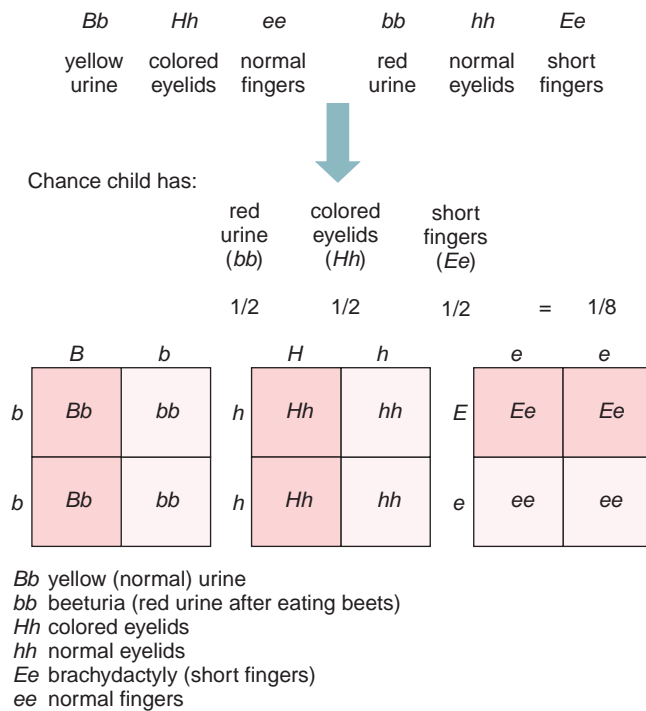
A Punnett square for *Rr* crossed to *Rr* shows that the probability of *Rr* plants producing *rr* progeny is 25 percent, or 1/4. Similarly, the chance of two *Yy* plants producing a *yy* plant is 1/4. Therefore, the chance of dihybrid parents (*RrYy*) producing homozygous recessive (*rryy*) offspring is 1/4 multiplied by 1/4, or 1/16. Now consult the 16-box Punnett square for Mendel's dihybrid cross again (**figure 4.10**). Only one of the 16 boxes is *rryy*, just as the product rule predicts. **Figure 4.12** shows how probability and Punnett squares can be used to predict offspring genotypes and phenotypes for three human traits simultaneously.

Until recently, Mendel's second law has not been as useful in medical genetics as the first law, because not enough genes were identified to follow the transmission of two or more traits at a time. But human



**Figure 4.11 The product rule.**

genome information and DNA microarray technology are changing that picture. It is common now to screen for hundreds or thousands of alleles or expressed



**Figure 4.12 Using probability to track three traits.** A man with normal urine, colored eyelids, and normal fingers wants to have children with a woman who has red urine after she eats beets, normal eyelids, and short fingers. The chance that a child of theirs will have red urine after eating beets, colored eyelids, and short fingers is  $1/8$ .

genes at once. The increasingly computational nature of genetics in this century has produced an entirely new field called bioinformatics. So, in this sense, genetics is continuing the theme of mathematical analysis that Gregor Mendel began more than a century ago.

## Key Concepts

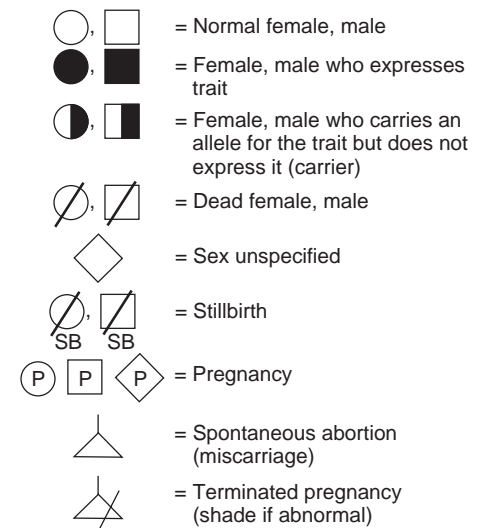
1. Mendel's law of independent assortment considers genes transmitted on different chromosomes.
2. In a dihybrid cross of heterozygotes for seed color and shape, Mendel saw a phenotypic ratio of 9:3:3:1. He concluded that transmission of one gene does not influence that of another.
3. Meiotic events explain independent assortment.
4. Punnett squares and probability can be used to follow independent assortment.
5. Knowing the human genome sequence has made it possible to analyze more than one gene at a time.

## 4.4 Pedigree Analysis

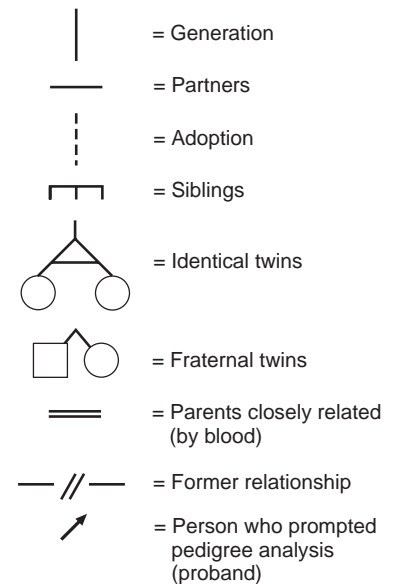
For researchers, families are tools, and the bigger the family the better—the more children in a generation, the easier it is to discern modes of inheritance. Geneticists use charts called **pedigrees** to display family relationships and to depict which relatives have specific phenotypes and, sometimes, genotypes. A human pedigree serves the same purpose as one for purebred dogs or cats or thoroughbred horses—it represents relationships and traits. A pedigree in genetics differs from a family tree in genealogy, and from a genogram in social work, in that it indicates disorders or traits as well as relationships. Pedigrees may also include molecular data, test results, and haplotypes (genes linked in segments on a chromosome).

A pedigree consists of lines that connect shapes. Vertical lines represent generations; horizontal lines that connect two shapes at their centers depict partners; shapes connected by vertical lines that are joined horizontally represent siblings. Squares indicate males; circles, females; and diamonds, individuals of unspecified sex. Roman

### Symbols



### Lines



### Numbers

Roman numerals = generations

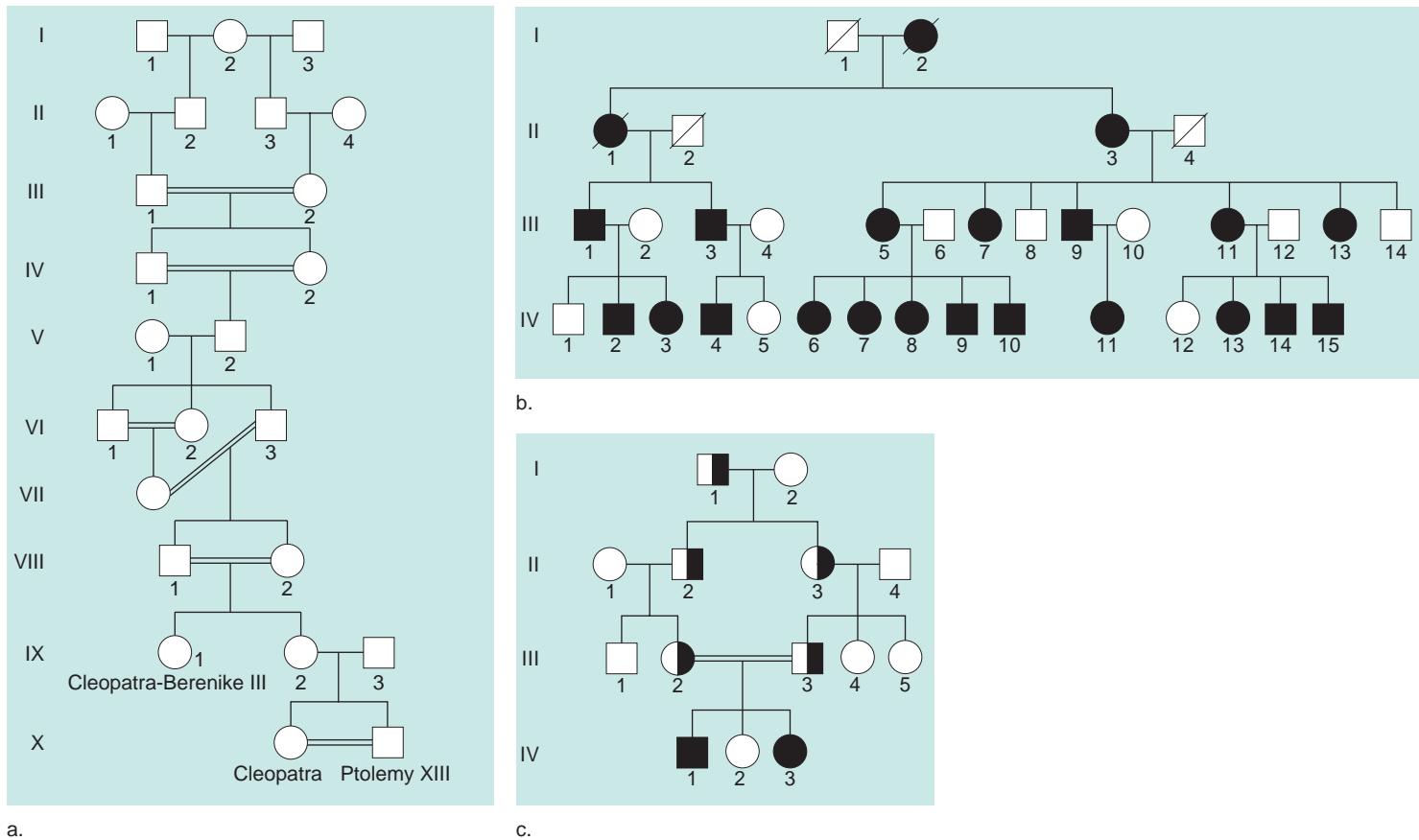
Arabic numerals = individuals in a generation

### Figure 4.13 Pedigree components.

Symbols representing individuals are connected to form pedigree charts, which display the inheritance patterns of particular traits.

numerals designate generations. Arabic numerals or names indicate individuals. **Figure 4.13** shows these and other commonly used pedigree symbols. Colored or shaded shapes indicate individuals who express a trait, and half-filled shapes are known





**Figure 4.14 Some unusual pedigrees.** (a) A partial pedigree of Egypt's Ptolemy dynasty shows only genealogy, not traits. It appears almost ladderlike because of the extensive inbreeding. From 323 B.C. to Cleopatra's death in 30 B.C., the family experienced one pairing between cousins related through half-brothers (generation III), four brother-sister pairings (generations IV, VI, VIII, and X), and an uncle-niece relationship (generations VI and VII). Cleopatra married her brother, Ptolemy XIII, when he was 10 years old! These marriage patterns were an attempt to preserve the royal blood. (b) In contrast to the Egyptian pedigree, a family with polydactyly (extra fingers and toes) extends laterally, with many children. (c) The most common form of consanguinity is marriage of first cousins. They share one set of grandparents, and therefore risk passing on the same recessive alleles to offspring.

carriers. A genetic counselor will often sketch out a pedigree while interviewing a client, then use a computer program and add test results that indicate genotypes.

## Pedigrees Then and Now

The earliest pedigrees were strictly genealogical, not indicating traits. **Figure 4.14** shows such a pedigree for a highly inbred part of the ancient Egyptian royal family. The term *pedigree* arose in the fifteenth century, from the French *pie de grue*, which means "crane's foot." Pedigrees at that time, typically depicting large families, showed parents linked by curved lines to their many offspring. The overall diagram often resembled a bird's foot.

One of the first pedigrees to trace an inherited illness was an extensive family tree

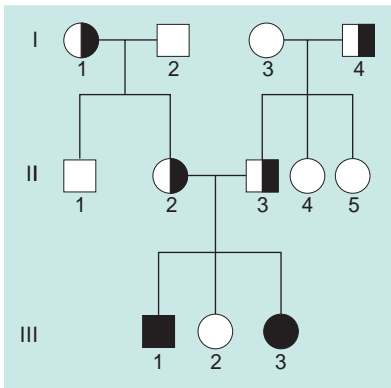
of several European royal families, indicating which members had the clotting disorder hemophilia (see figure 6.8). The mutant gene probably originated in Queen Victoria of England in the nineteenth century. In 1845, a genealogist named Pliny Earle constructed a pedigree of a family with colorblindness using musical notation—half notes for unaffected females, quarter notes for colorblind females, and filled-in and squared-off notes to represent the many colorblind males. In the early twentieth century, eugenicists tried to use pedigrees to show that traits such as criminality, feeble-mindedness, and promiscuity were the consequence of faulty genes.

Today, pedigrees are important both for helping families identify the risk of transmitting an inherited illness and as starting

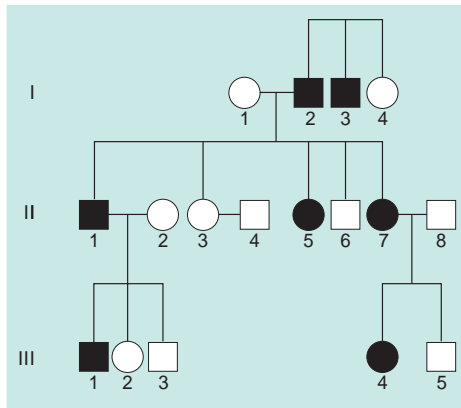
points for identifying a gene from the human genome sequence. People who have kept meticulous family records are invaluable in helping researchers follow the inheritance of particular genes in groups such as the Mormons and the Amish. Very large pedigrees can provide information on many individuals with a particular rare disorder. The researchers can then search affected individuals' DNA to identify a particular sequence they have all inherited that is not found in healthy family members. This is where the causative mutation lies. Discovery of the gene that causes HD, for example, took researchers to a remote village in Venezuela to study an enormous family. The gene was eventually traced to a Portuguese sailor who introduced the mutation in the nineteenth century.

## Pedigrees Display Mendel's Laws

Visual learners can easily “see” a mode of inheritance in a pedigree. Consider a pedigree for an autosomal recessive trait, albinism. Homozygous recessive individuals in the third ( $F_2$ ) generation lack an enzyme necessary to manufacture the pigment melanin and, as a result, hair and skin are very pale (**figure 4.15**). Their parents are inferred to be heterozygotes (carriers). One partner from each pair of grandparents must also be a carrier. Carriers can sometimes be identified using a carrier test, inferred from family history, or deduced from the DNA sequence.



**Figure 4.15 A pedigree for an autosomal recessive trait.** Albinism affects males and females and can skip generations, as it does here in generations I and II. The homozygous recessive individual lacks an enzyme needed to produce melanin, which colors the eyes, skin, and hair.



**Figure 4.16 A pedigree for an autosomal dominant trait.** Autosomal dominant traits do not skip generations.

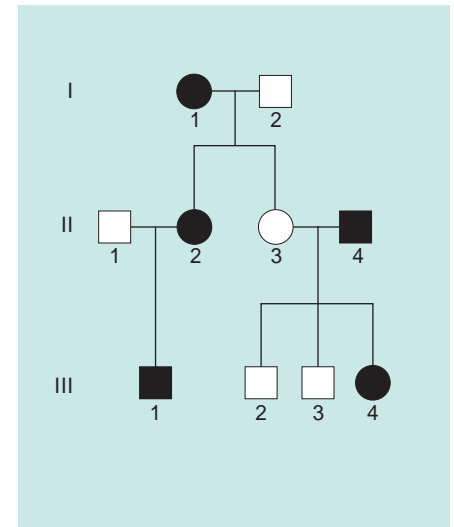
An autosomal dominant trait does not skip generations and can affect both sexes. A typical pedigree for an autosomal dominant trait has some squares and circles filled in to indicate affected individuals in each generation (**figure 4.16**).

A pedigree may be inconclusive, which means that either autosomal recessive or autosomal dominant inheritance can explain the pattern of filled-in symbols. **Figure 4.17** shows one such pedigree, for a type of hair loss called alopecia areata (OMIM 104000). According to the pedigree, this trait can be passed in an autosomal dominant mode because it affects both males and females and is present in every generation. However, the pedigree can also depict autosomal recessive inheritance if the individuals represented by unfilled symbols are carriers. Inconclusive pedigrees tend to arise when families are small and the trait is not severe enough to impair fertility.

### Solving a Problem: Conditional Probability

Often genetic counselors are asked to predict the probability that a condition will occur in a particular individual. Mendel's laws, pedigrees, and Punnett squares provide clues, as do logic and common sense. Consider the family depicted in **figure 4.18**.

Michael Stewart has sickle cell disease, which is autosomal recessive. His unaffected parents, Kate and Brad, must each be heterozygotes (carriers). Michael's sister,

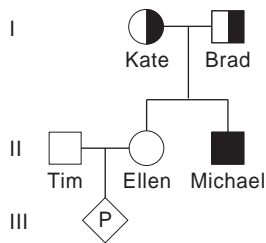


**Figure 4.17 An inconclusive pedigree.** This pedigree could account for an autosomal dominant trait or an autosomal recessive trait that does not prevent affected individuals from having children. (Unfilled symbols could represent carriers.)

Ellen, also healthy, is expecting her first child. Ellen's husband, Tim, has no family history of sickle cell disease. Ellen wants to know the risk that her child will inherit the mutant allele from her and be a carrier.

Ellen's request raises two questions. First, what is the risk that she herself is a carrier? Because Ellen is the product of a monohybrid cross, and we know that she is not homozygous recessive, she has a 2 in 3 chance of being a carrier, as the Punnett square indicates. If Ellen is a carrier, what is the chance that she will pass the mutant allele to an offspring? It is 1 in 2, because she has two copies of the gene, and according to Mendel's first law, only one allele goes into each gamete.

To calculate the overall risk to Ellen's child, we can apply the product rule and multiply the probability that Ellen is a carrier by the chance that, if she is, she will pass the mutant allele on. This result, following two events, is a conditional probability, because the likelihood of the second event—the child being a carrier—depends upon the first event—that Ellen is a carrier. If we assume Tim is not a carrier, Ellen's chance of giving birth to a child who carries the mutant allele is therefore  $2/3$  times  $1/2$ , which equals  $2/6$ , or  $1/3$ . Ellen thus has a



a. Ellen's brother, Michael, has sickle cell disease.

		Kate	
		S	s
Brad	S	SS	Ss
	s	Ss	ss

b. Probability that Ellen is a carrier:  $\frac{2}{3}$

		Ellen	
		S	s
Tim	S	SS	Ss
	s	SS	Ss

c. If Ellen is a carrier, chance that fetus is a carrier:  $\frac{1}{2}$

Total probability =  $\frac{2}{3} \times \frac{1}{2} = \frac{1}{3}$

**Figure 4.18 Making predictions.** Ellen's brother, Michael, has sickle cell disease (a). Ellen wonders if her fetus has inherited the sickle cell allele from her. First, she must calculate the chance that she is a carrier. The Punnett square in (b) shows that this risk is 2 in 3. (She must be genotype SS or Ss, but cannot be ss because she does not have the disease.) The risk that the fetus is a carrier, assuming that the father is not a carrier, is half Ellen's risk of being a carrier, or 1 in 3 (c).

theoretical 1 in 3 chance of giving birth to a child who is a carrier for sickle cell disease.

Pedigrees work well in theory but may be difficult to construct or interpret in practice

for several reasons. People sometimes hesitate to supply information because they are embarrassed by symptoms affecting behavior or mental stability. Family relationships

can be complicated by adoption, children born out of wedlock, serial relationships, blended families, and assisted reproductive technologies such as surrogate mothers and intrauterine insemination by donor (see chapter 21). Moreover, many people cannot trace their families back more than three or four generations, so they lack sufficient evidence to reveal a mode of inheritance. Still, the pedigree remains a powerful way to see, at a glance, how a trait passes from generation to generation—just as Gregor Mendel did with peas.

## Key Concepts

1. Pedigrees depict family relationships and the transmission of inherited traits. Squares represent males, and circles, females; horizontal lines link partners, vertical lines show generations, and elevated horizontal lines depict siblings. Heterozygote symbols are half-shaded, and symbols for individuals who express a trait are completely shaded.
2. Pedigrees can reveal modes of inheritance. Along with Punnett squares, they are tools that apply Mendel's laws to predict the recurrence risks of inherited disorders or traits.

# Summary

## 4.1 Following the Inheritance of One Gene—Segregation

1. Gregor Mendel described the two basic laws of inheritance using pea plant crosses. The laws, which derive from the actions of chromosomes during meiosis, apply to all diploid organisms.
2. Mendel used a statistical approach to investigate why some traits seem to disappear in the hybrid generation. The **law of segregation** states that alleles of a gene are distributed into separate gametes during meiosis. Mendel demonstrated this using seven traits in pea plants.
3. A diploid individual with two identical alleles of a gene is **homozygous**. A

**heterozygote** has two different alleles of a gene. A gene may have many alleles.

4. A **dominant** allele masks the expression of a **recessive** allele. An individual may be homozygous dominant, homozygous recessive, or heterozygous.
5. Mendel found that when he crossed two true-breeding types, then bred the resulting hybrids to each other, the two variants of the trait appeared in a 3:1 phenotypic ratio. Crossing these progeny further revealed a genotypic ratio of 1:2:1.
6. A **Punnett square** follows the transmission of alleles and is based on probability.

## 4.2 Single-Gene Inheritance in Humans

7. **Modes of inheritance** enable geneticists to predict phenotypes. In **autosomal dominant** inheritance, males and females may be affected, and the trait does not skip generations. Inheritance of an **autosomal recessive** trait may affect either males or females and may skip generations. Autosomal recessive conditions are more likely to occur in families with **consanguinity**. Recessive disorders tend to be more severe and cause symptoms earlier than dominant disorders.



8. Genetic problems can be solved by tracing alleles as gametes form and then combine in a new individual.
9. Dominance and recessiveness reflect how alleles affect the abundance or activity of the gene's protein product.

#### 4.3 Following the Inheritance of Two Genes—Independent Assortment

10. Mendel's second law, the **law of independent assortment**, follows the

transmission of two or more genes on different chromosomes. A random assortment of maternally and paternally derived chromosomes during meiosis results in gametes that have different combinations of these genes.

11. The chance that two independent genetic events will both occur is equal to the product of the probabilities that each event will occur. This product rule is useful in calculating the risk that individuals will inherit a particular genotype and in following the inheritance of genes on different chromosomes.

#### 4.4 Pedigree Analysis

12. A **pedigree** is a chart that depicts family relationships and patterns of inheritance for particular traits. A pedigree can be inconclusive.

## Review Questions

1. How does meiosis explain Mendel's laws of segregation and independent assortment?
2. How was Mendel able to derive the two laws of inheritance without knowing about chromosomes?
3. Distinguish between
  - a. autosomal recessive and autosomal dominant inheritance.
  - b. Mendel's first and second laws.
  - c. a homozygote and a heterozygote.
4. Why would Mendel's results for the dihybrid cross have been different if the genes for the traits he followed were located near each other on the same chromosome?
5. Why are extremely rare autosomal recessive disorders more likely to appear in families in which blood relatives have children together?
6. How does the pedigree of the ancient Egyptian royal family in figure 4.14a differ from a pedigree a genetic counselor might use today?
7. People who have Huntington disease inherit one mutant and one normal allele. How would an individual homozygous dominant for the condition be conceived?
8. What is the probability that two individuals with an autosomal recessive trait, such as albinism, will have a child with the same genotype and phenotype as they do?

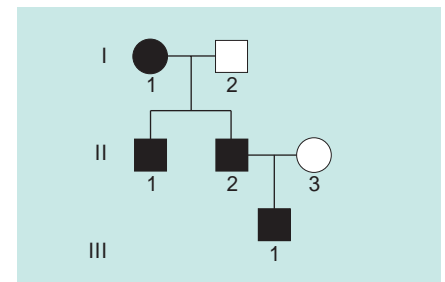
## Applied Questions

1. Predict the phenotypic and genotypic ratios for crossing the following pea plants:
  - a. short  $\times$  short
  - b. short  $\times$  true-breeding tall
  - c. true-breeding tall  $\times$  true-breeding tall
2. What are the genotypes of the pea plants that would have to be bred to yield one plant with restricted pods for every three plants with inflated pods?
3. If pea plants with all white seed coats are crossed, what are the possible phenotypes of their progeny?
4. Pea plants with restricted yellow pods are crossed to plants that are true-breeding for inflated green pods. The  $F_1$  are then crossed. Derive the phenotypic and genotypic ratios for the  $F_2$  generation.
5. A gene that the media described as the "bad hair day" gene is technically called

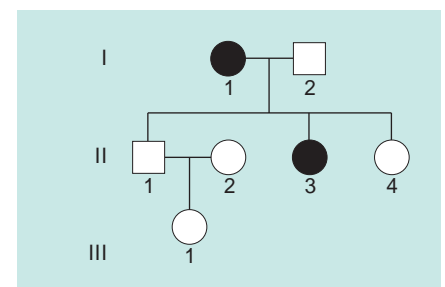
frizzled (OMIM 601723), named for its well-studied counterparts in fruit flies and mice. Frizzled is inherited as an autosomal recessive trait, and the gene is on chromosome 2. A gene for "strikingly red hair," also autosomal recessive, is on chromosome 4 (OMIM 266300).

Gina Rollins and Spencer Davis have boring, straight brown hair. They are amazed to discover that each has a mother (Inga and Magda) with strikingly red, frizzled hair. Their fathers, Ralph and Fred, both have boring, straight brown hair. If Gina and Spencer have children, what is the probability that each will have either trait, both traits, or neither?

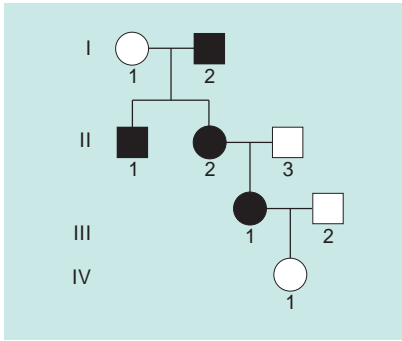
6. Following are four pedigrees depicting families with tetramelicmonodactyly, in which the hands and feet have only the smallest digit. What is the most likely mode of inheritance? Cite a reason for your answer.



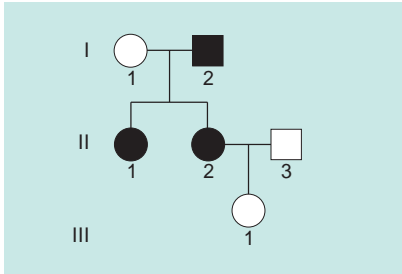
a.



b.

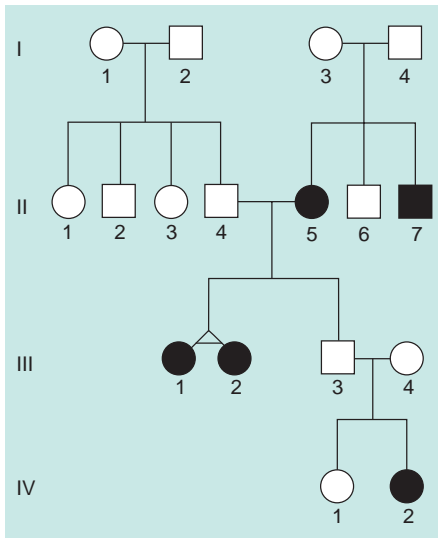


c.



d.

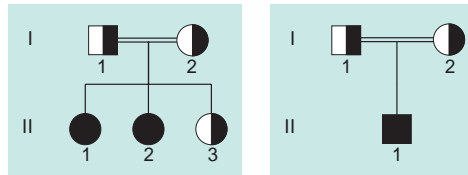
7. Draw a pedigree to depict the following family: One couple has a son and a daughter with normal skin pigmentation. Another couple has one son and two daughters with normal skin pigmentation. The daughter from the first couple has three children with the son of the second couple. Their son and one daughter have albinism (OMIM 203100); their other daughter has normal skin pigmentation.
8. Chands syndrome (OMIM 214350) is an autosomal recessive condition characterized by very curly hair, underdeveloped nails, and abnormally shaped eyelids. In the following pedigree, which individuals must be carriers?



Chands syndrome

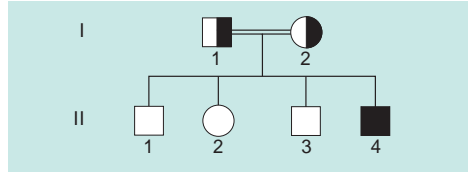
9. Caleb has a double row of eyelashes (OMIM 126300), which he inherited from his mother as a dominant trait. His maternal grandfather is the only other relative to have the trait. Veronica, a woman with normal eyelashes, falls madly in love with Caleb, and they marry. Their first child, Polly, has normal eyelashes. Now Veronica is pregnant again and hopes they will have a child who has double eyelashes. What chance does a child of Veronica and Caleb have of inheriting double eyelashes? Draw a pedigree of this family.

10. Peeling skin syndrome (OMIM 270300) causes the outer skin layer to fall off on the upper surfaces of the hands and feet. The pedigrees depict three families with this condition. What do they share that might explain the appearance of this otherwise rare condition?



a.

b.

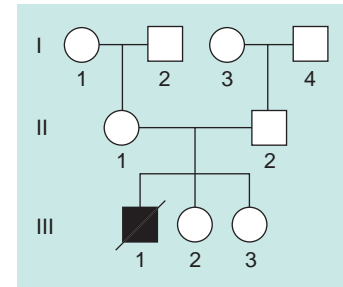


c.

11. The child in figure 4.12 who has red urine after eating beets, colored eyelids,

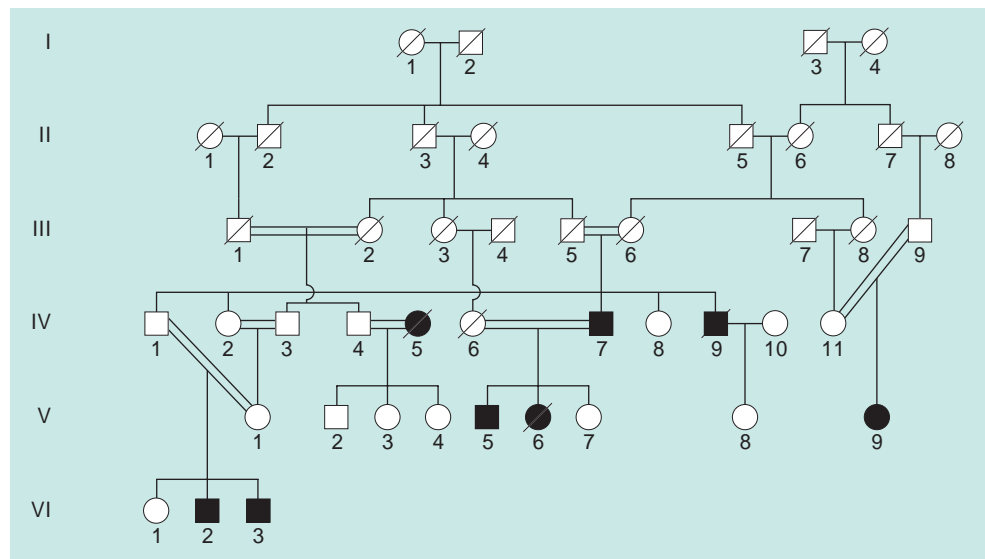
and short fingers, is of genotype  $bbHhEe$ . The genes for these traits are on different chromosomes. If he has children with a woman who is a trihybrid for each of these genes, what are the expected genotypic and phenotypic ratios for their offspring?

12. In this pedigree, individual III-1 died at age two of Tay-Sachs disease, an autosomal recessive disorder. Which other family members must be carriers, and which could be?



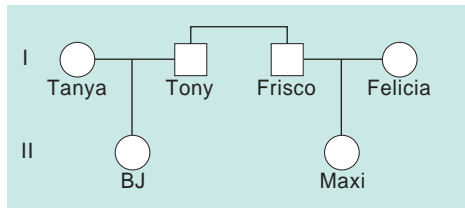
Tay-Sachs disease

13. Sclerosteosis (OMIM 269500) causes overgrowth of the skull and jaws that produces a characteristic face, gigantism, facial paralysis, and hearing loss. The overgrowth of skull bones can cause severe headaches and even sudden death. In this pedigree for a family with sclerosteosis:
- What is the relationship between the individuals who are connected by slanted double lines?
  - Which individuals in the pedigree must be carriers of this autosomal recessive condition?



Sclerosteosis

14. On “General Hospital,” six-year-old Maxie suffered from Kawasaki syndrome, an inflammation of the heart. She desperately needed a transplant, and received one from BJ, who died in a bus accident. Maxi and BJ had the same unusual blood type, which is inherited. According to this pedigree, how are Maxi and BJ related?



15. A man has a blood test for Tay-Sachs disease and learns that he is a carrier. His body produces half the normal amount of an enzyme. Why doesn't he have symptoms?

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 4** and **Web Activities** to find the website links needed to complete the following activities.

16. Go to the website for the National Organization for Rare Disorders. Identify an autosomal recessive disorder and an autosomal dominant disorder. Create a family for each one, and describe transmission of the disease over three generations.
17. Go to the website for Gene Gateway—Exploring Genes and Genetic Disorders. Select two disorders or traits that would demonstrate independent assortment if present in the same family, and two that would not.
18. Many software programs are available that construct pedigrees, even for pets. A free one is at [www.hhs.gov/familyhistory](http://www.hhs.gov/familyhistory). It only follows a few diseases, but is very helpful for displaying relationships. PowerPoint can also be used to construct a pedigree. Use these or other resources, or old-fashioned pencil and paper, to construct a pedigree for your own family.

### Case Studies and Research Results

19. On the daytime drama “The Young and the Restless,” several individuals suffer from SORAS, which stands for “soap opera rapid aging syndrome.” It is not listed in OMIM. In SORAS, a young child is sent off to boarding school and returns three months later an angry teenager. In the Newman family, siblings Nicholas and Victoria aged from ages 6 and 8 years, respectively, to 16 and 18 years within a few months. Their parents, Victor and Nikki, are curiously not affected; in fact, they never seem to age at all.

- What is the mode of inheritance of the rapid aging disorder affecting Nicholas and Victoria?
  - How do you know what the mode of inheritance is?
  - Draw a pedigree to depict this portion of the Newman family.
20. More than a dozen recessive illnesses that are very rare in most of the world are fairly common among the Bedouin people who live in the Negev desert area of Israel. More than 65 percent of Bedouins marry their first or second cousins. This practice helped enable the group to survive a nomadic existence in the harsh environment in the past. Recently, two physicians and a geneticist have set up a service for the Bedouins that enables people wishing to marry to take genetic tests to learn if they are carriers for the same diseases. Prenatal testing has also been introduced to provide the option of terminating pregnancies that would otherwise lead to the births of children who would die of a recessive disorder in early childhood.

Discuss the pros and cons of introducing genetic testing in this community, including your opinion on whether medical science should interfere with a society's long-held cultural practices.

21. In the United States, some people do not take predictive genetic tests, such as the one for HD, because they fear denial of health insurance or other discrimination. Use of HD testing was studied in Canada, where health care is nationalized and a prediction of HD could not deny anyone coverage. The study found that older people were the ones who chose

to be tested, citing a desire to have the information to plan their financial futures.

- Why do you think younger people might not want the predictive HD test?
  - What might be an advantage of a young person taking the test?
22. The Cleaver family awaited the birth of Claudette's puppies with great anticipation. But shortly after the standard poodle gave birth to 6 pups, two of them, a male and a female, developed seizures and died. One of the surviving pups, Sylvester, was bred when he was a year old to Minuette, who was an offspring of Sylvester's father, Otis. Alas, one of Minuette's four pups also died of the canine seizure disorder.
- Draw a pedigree for the poodle family.
  - What is the mode of inheritance of the canine seizure disorder?
  - What advice would you give to the Cleavers about successfully breeding their poodles in the future?
23. Ryder is a 6-month-old in seemingly good health, except that he is very sensitive to bright light. When the light is turned on in the nursery, or he's taken outside, he squints and cries, rubbing his eyes. He calms down when taken out of the light. His dad, Chris, is also sensitive to very bright light, but fortunately he is a rock star so is expected to wear dark glasses all the time. He barely notices the condition. Kate, Ryder's mom, mentioned the light sensitivity at a well-baby visit to the pediatrician, who examined Ryder's eyes carefully. She saw tiny white flecks scattered all over his corneas. The doctor thought it might be corneal fleck dystrophy (OMIM 121850), so she examined Kate and Chris's eyes too. Chris had the same white flecks. On discussing the finding with the extended family, Chris and Kate learned that Chris's mom, Golda, had the flecks but his dad Curtis didn't, and that his sister Emily had them, too, but his brother Dan didn't.
- What is a mode of inheritance that explains the pattern of corneal fleck dystrophy in Ryder's family?
  - Draw a pedigree for the family.
  - What is the risk that a child of Ryder's will inherit the condition?



# A Second Look

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1. A student reads about Alex Deford and concludes that the parents must be relieved that their next three children will not have CF, thanks to Mendel's first law. How has the student misinterpreted the law?
2. What would need to be true for Frank Deford's sister to face the same risk of having a child with CF as Frank does?
3. If another child of the Defords is healthy, what might her genotype be?

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

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Carnosinemia  
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# Beyond Mendel's Laws

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## THE MANY FACES OF ALKAPTONURIA

Pat Wright became aware of her alkaptonuria (OMIM 203500) at age 15, when she suffered back spasms. As she got older, her spine continued to degenerate, and the cartilage in her left knee also broke down. She managed to have five children and to teach for 26 years, but retired on disability at age 57.

Wright's medical records noted a "harmless" metabolic disorder. Her parents had taken her to the doctor after noticing dark-stained diapers. The pediatrician, suspecting alkaptonuria, sent a blackened diaper to geneticists, who diagnosed the disorder—but it was never explained well to the parents, who were carriers. Alkaptonuria was one of four disorders English physician Sir Archibald Garrod described in 1902 as "inborn errors of metabolism."

Wright didn't hear a name for her condition until 1997, when the surgeon who was replacing her knee was amazed to find blackened cartilage around the joint. This explained the pains, stained diapers, and even the dark blue-gray color of Wright's ears, he told her, as well as her hearing loss, gallstones, and heart valve damage.

In alkaptonuria, a single mutation causes several symptoms because the encoded protein is present in different body parts. Specifically, deficiency of an enzyme leads to buildup of an acid that reacts to produce a black pigment that is deposited in urine, nails, skin, and cartilage. When urine is exposed to oxygen, it turns black. A mutation that is associated with several symptoms is one of the ways that single-gene inheritance may not be as straightforward as it seems.



Blackened nails are one sign of alkaptonuria, an inborn error of metabolism.

The transmission of inherited traits is not always as straightforward as Mendel’s pea experiments indicated. This chapter examines extensions of and exceptions to Mendel’s laws. Single-gene inheritance can seem complicated.

### 5.1 When Gene Expression Appears to Alter Mendelian Ratios

Mendel’s crosses yielded offspring that were easily distinguished from each other. A pea is either yellow or green; a plant tall or short. For some characteristics, though, offspring classes do not occur in the proportions that Punnett squares or probabilities predict. In other cases, transmission patterns of a visible trait are not consistent with a mode of inheritance, such as autosomal recessive or autosomal dominant. In these instances, Mendel’s laws operate, and the underlying genotypic ratios persist, but either the nature of the phenotype or influences from other genes or the environment alter phenotypic ratios—that is, what is actually seen. Following are several circumstances in which phenotypic ratios appear to contradict Mendel’s laws—although the laws actually still apply.

### Lethal Allele Combinations

A genotype (allele combination) that causes death is, by definition, lethal. Death from genetic disease can occur at any stage of development or life. Some of the disorders in table 3.3 are lethal. Tay-sachs disease, for example, is lethal by age 3 or 4; HD may not be lethal until late middle age. In a population and evolutionary sense, a lethal genotype has a more specific meaning—it causes death before the individual can reproduce, which prevents passage of genes to the next generation.

In organisms used in experiments, such as fruit flies, pea plants, or mice, lethal allele combinations remove an expected progeny class following a specific cross. For example, a cross of two heterozygous flies, in which the homozygous recessive progeny die as embryos, leaves only heterozygous and homozygous dominant adult fly offspring.

In humans, early-acting lethal alleles cause spontaneous abortion (technically called “miscarriages” if they occur after the embryonic period). When a man and woman each carries a recessive lethal allele for the same gene, each pregnancy has a 25 percent chance of spontaneously aborting—a proportion representing the homozygous recessive class. Sometimes a double dose of a dominant allele is lethal, as is the case for Mexican hairless dogs (figure 5.1). Inheriting one dominant allele confers the coveted hairlessness trait, but inheriting two dominant alleles is lethal to the unlucky embryo. Breeders cross hairless to hairy (“powderpuff”) dogs, rather than hairless to hairless, to avoid losing the lethal homozygous dominant class—a quarter

of the pups. In humans, achondroplastic dwarfism is similarly lethal in the homozygous dominant condition.

### Multiple Alleles

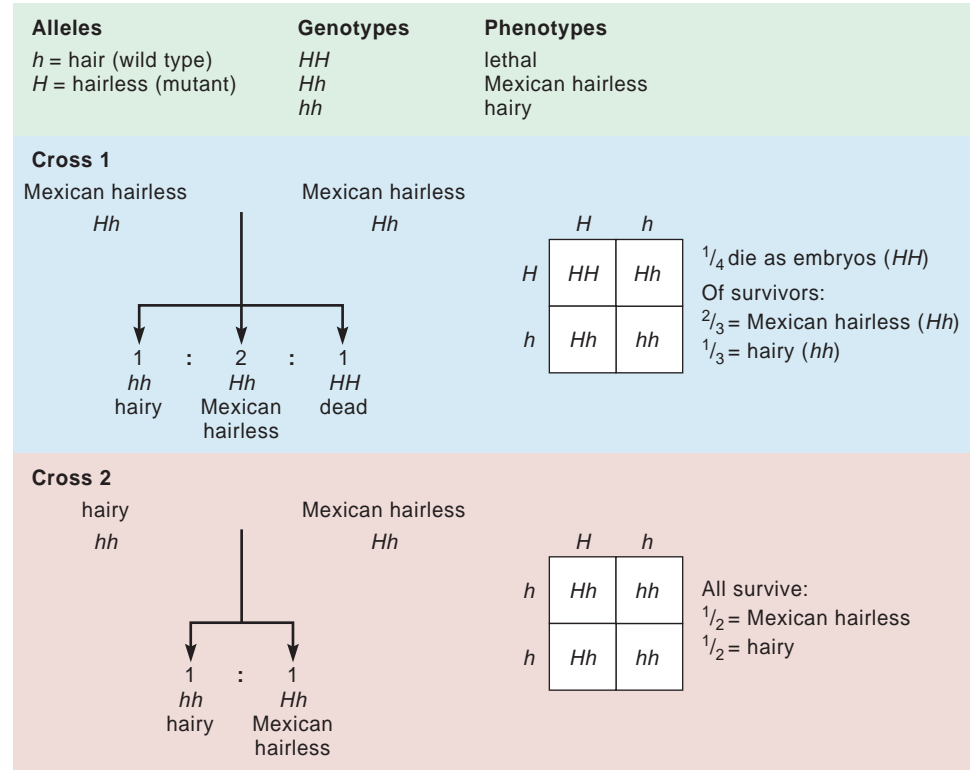
An individual has two alleles for any autosomal gene—one allele on each homolog. However, a gene can exist in more than two allelic forms in a population because it can mutate in many ways. That is, the sequence of hundreds of DNA bases that makes up a gene can be altered in many ways. Different allele combinations can produce variations in the phenotype.

It would be very useful if testing for a particular genotype could always enable physicians to predict the course of an

**Figure 5.1 Lethal alleles.** (a) This Mexican hairless dog has inherited a dominant allele that makes it hairless. Inheriting two such dominant alleles is lethal to embryos. (b) Breeders cross Mexican hairless dogs to hairy (“powderpuff”) dogs to avoid dead embryos and stillbirths that represent the HH genotypic class.



a.



b.



illness. However, this is often difficult because other genes and environmental effects can modify the phenotype, a point we return to soon. However, two disorders for which allele identification *can* predict severity and types of symptoms are phenylketonuria (PKU) and cystic fibrosis.

In PKU a deficient or absent enzyme causes the amino acid phenylalanine to build up in brain cells. Hundreds of mutant alleles combine to form four basic phenotypes:

- classic PKU with profound mental retardation
- moderate PKU
- mild PKU
- asymptomatic PKU, with excretion of excess phenylalanine in urine

Eating a special diet extremely low in phenylalanine allows normal brain development. Knowing the allele combination can guide how strict the diet need be, and how long it must continue.

Multiple alleles are considered in carrier testing for CF, which is done routinely in early pregnancy. When the CF gene was discovered in 1989, researchers identified one mutant allele, called  $\Delta F508$ , that causes about 70 percent of cases in many populations. As the allele list grew, researchers discovered that not all allele combinations cause the same symptoms. People homozygous for  $\Delta F508$  are very ill, with frequent serious respiratory infections, very sticky mucus in the lungs, and poor weight gain due to an impaired pancreas. Another genotype increases susceptibility to bronchitis and pneumonia, and another causes only absence of the vas deferens. Genetic tests probe panels of CF mutations that are the most common in a patient's ethnic group, maximizing the likelihood of detecting carriers and avoiding the cost of testing for 1,500<sup>+</sup> alleles. If a pregnant woman has a disease-causing allele, then the father-to-be is tested, and if he has a mutant allele too, then the fetus may be tested to see if it has inherited the disease.

## Different Dominance Relationships

With complete dominance, one allele is expressed, while the other isn't. With **incomplete dominance**, the heterozygous

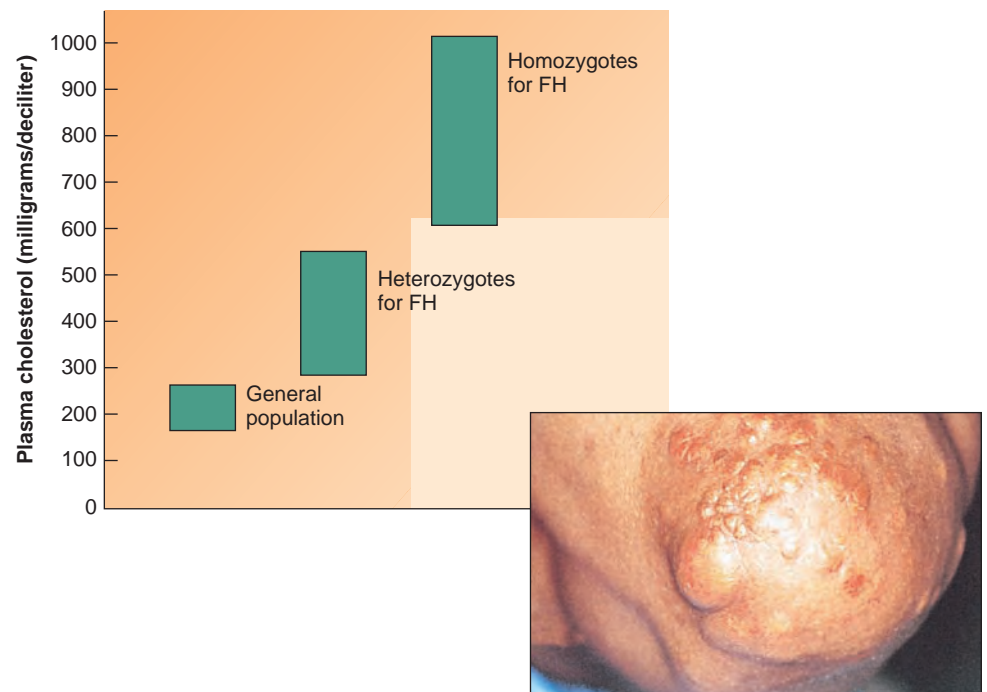
phenotype is intermediate between that of either homozygote.

In a sense, enzyme deficiencies in which a threshold level is necessary for health illustrate both complete and incomplete dominance—depending upon how one evaluates the phenotype. For example, on a whole-body level, Tay-Sachs disease displays complete dominance because the heterozygote (carrier) is as healthy as a homozygous dominant individual. However, if phenotype is based on enzyme level, then the heterozygote is intermediate between the homozygous dominant (full enzyme level) and homozygous recessive (no enzyme). Half the normal amount of enzyme is sufficient for health, which is why at the whole-person level, the wild type allele is completely dominant. For many genes, researchers can now measure the expression levels of various genotypes, demonstrating that even heterozygotes whose phenotypes are the same as those of homozygotes are distinctive at the biochemical level. Often, they produce half the normal amount of a protein, but this is sufficient for health.

Familial hypercholesterolemia (FH) is an example of incomplete dominance in humans that can be observed on both the molecular and whole-body levels. A person with two disease-causing alleles lacks receptors on liver cells that take up the low density lipoprotein (LDL) form of cholesterol from the bloodstream. A person with one disease-causing allele has half the normal number of receptors. Someone with two wild type (the most common) alleles has the normal number of receptors. **Figure 5.2** shows how measurement of plasma cholesterol reflects these three genotypes. The phenotypes parallel the number of receptors—those with two mutant alleles die as children of heart attacks, those with one mutant allele may suffer heart attacks in young adulthood, and those with two wild type alleles do not develop this inherited form of heart disease.

Different alleles that are both expressed in a heterozygote are **codominant**. The ABO blood group is based on the expression of codominant alleles.

Blood types are determined by the patterns of cell surface molecules on red blood



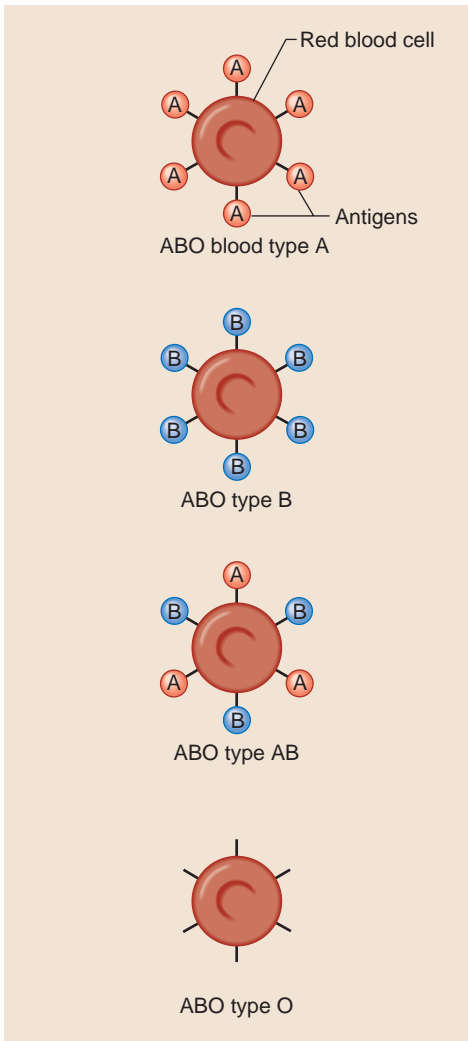
**Figure 5.2 Incomplete dominance.** A heterozygote for familial hypercholesterolemia (FH) has approximately half the normal number of cell surface receptors in the liver for LDL cholesterol. An individual with two mutant alleles has the severe form of FH, with liver cells that totally lack the receptors. As a result, serum cholesterol level is very high. The photograph shows cholesterol deposits on the elbow of an affected young man.

cells. Most of these molecules are proteins embedded in the plasma membrane with attached sugars that extend from the cell surface. The sugar is the antigen, which is the molecule that the immune system recognizes. People who belong to blood group A have an allele that encodes an enzyme that adds a final piece to a certain sugar to produce antigen A. In people with blood type B, the allele and its encoded enzyme are slightly different, which causes a different piece to attach to the sugar, producing antigen B. People in blood group AB have both antigen types. Blood group O reflects yet a third allele of this gene. It is missing just one DNA nucleotide, but this drastically changes the encoded enzyme in a way that robs the sugar chain of its final piece (figure 5.3).

The A and B alleles are codominant, and both are completely dominant to O. Considering the genotypes reveals how these interactions occur. In the past, ABO blood types have been described as variants of a gene called “*I*,” although OMIM now abbreviates the designations. The older *I* system is easier to understand (table 5.1). (“*I*” stands for isoagglutinin.) The three alleles are *I*<sup>A</sup>, *I*<sup>B</sup>, and *i*. People with blood type A have antigen A on the surfaces of their red blood cells, and may be of genotype *I*<sup>A</sup>*I*<sup>A</sup> or *I*<sup>A</sup>*i*. People with blood type B have antigen B on their red blood cell surfaces, and may be of genotype *I*<sup>B</sup>*I*<sup>B</sup> or *I*<sup>B</sup>*i*. People with the rare blood type AB have both antigens A and B on their cell surfaces, and are genotype *I*<sup>A</sup>*I*<sup>B</sup>. People with blood type O have neither antigen, and are genotype *ii*.

Television program plots often misuse ABO blood type terminology, assuming

Table 5.1 The ABO Blood Group		
Genotypes	Phenotypes	
	Antigens on Surface	ABO Blood Type
<i>I</i> <sup>A</sup> <i>I</i> <sup>A</sup>	A	Type A
<i>I</i> <sup>A</sup> <i>i</i>	A	Type A
<i>I</i> <sup>B</sup> <i>I</i> <sup>B</sup>	B	Type B
<i>I</i> <sup>B</sup> <i>i</i>	B	Type B
<i>I</i> <sup>A</sup> <i>I</i> <sup>B</sup>	AB	Type AB
<i>ii</i>	None	Type O

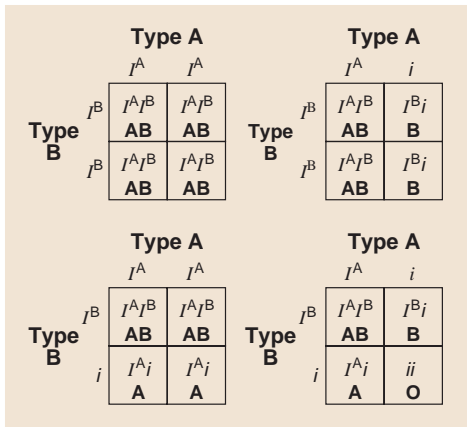


**Figure 5.3 ABO blood types illustrate codominance.** ABO blood types are based on antigens on red blood cell surfaces. The size of the A and B antigens is greatly exaggerated in this drawing.

that a child’s ABO type must match that of one parent. This is not true, because a person with type A or B blood can be heterozygous. A person who is genotype *I*<sup>A</sup>*i* and a person who is *I*<sup>B</sup>*i* can jointly produce offspring of any ABO genotype or phenotype, as figure 5.4 illustrates.

### Epistasis

Mendel’s laws can appear not to operate when one gene masks or otherwise affects the phenotype of another. This phenomenon is called **epistasis**. It refers to interaction between different genes, not between the alleles of the same gene.



**Figure 5.4 Codominance.** The *I*<sup>A</sup> and *I*<sup>B</sup> alleles of the *I* gene are codominant, but they follow Mendel’s law of segregation. These Punnett squares follow the genotypes that could result when a person with type A blood has children with a person with type B blood.

In epistasis, the blocked gene is expressed normally, but the product of the controlling, or epistatic, gene inactivates it or removes a structure needed for it to contribute to the phenotype. Obvious examples of epistasis are a hairless gene in dogs and a spineless gene in cucumbers. Genes responsible for coloring dog hairs or cucumber spines can’t act if those hairs and spines aren’t present. An epistatic interaction seen in many species is albinism, in which one gene blocks the action of genes whose products confer color.

A more complex example of epistasis is a blood type called the Bombay phenotype. It results from an interaction between a gene called *H* and the *I* gene that confers ABO blood type. The *H* gene controls the placement of a molecule to which antigens A and B attach on red blood cell surfaces. In a person of genotype *ii*, that molecule isn’t made, so the A and B antigens have no way to attach to the red blood cell surface. The A and B antigens fall off—and the person tests as type O blood, although any ABO genotype is possible.

### Penetrance and Expressivity

The same allele combination can produce different degrees of a phenotype in different individuals because a gene does not act

alone. Nutrition, exposure to toxins, stress, illnesses, and actions of other genes may influence the expression of most genes. For example, two individuals who have the most severe CF genotype may have different clinical experiences. One may be much sicker because she also inherited genes predisposing her to develop asthma and respiratory allergies. Even identical twins with the same genetic disease may be affected to different degrees due to environmental influences.

Many single-gene traits and illnesses have distinctive phenotypes, despite all of these influences. The terms *penetrance* and *expressivity* describe degrees of expression of a single gene. **Penetrance** refers to the all-or-none expression of a genotype; **expressivity** refers to severity or extent.

An allele combination that produces a phenotype in everyone who inherits it is completely penetrant. Huntington disease (see Bioethics: Choices for the Future in chapter 4) is completely penetrant—all who inherit the mutant allele will develop symptoms if they live long enough, although symptoms may not begin until late in life.

A genotype is incompletely penetrant if some individuals do not express the phenotype (have no symptoms). Polydactyly (see figure 1.5) is incompletely penetrant. Some people who inherit the dominant allele have more than five digits on a hand or foot. Yet others who must have the allele, because they have an affected parent and child, have ten fingers and toes. Penetrance is described numerically. If 80 of 100 people who inherit the dominant polydactyly allele have extra digits, the genotype is 80 percent penetrant.

A phenotype is variably expressive if symptoms vary in intensity in different people. One person with polydactyly might have an extra digit on both hands and a foot, but another might have just one extra fingertip. Therefore, polydactyly is both incompletely penetrant and variably expressive.

It is hard to imagine how other genes or the environment can influence the numbers of fingers or toes. For familial hypercholesterolemia, variable expressivity reflects greater influence of other genes that regulate lipid levels in the blood and the environment (see figure 5.2). FH heterozygotes develop heart disease due to high serum cholesterol in middle adulthood.

Healthful diet and exercise habits as well as lipid-lowering drugs can delay symptom onset.

## Pleiotropy

A single-gene disorder with many symptoms, or a gene that controls several functions or has more than one effect, is termed **pleiotropic**. Such conditions can be difficult to trace through families because people with different subsets of symptoms may appear to have different disorders. This is the case for porphyria variegata, an autosomal dominant, pleiotropic, inborn error of metabolism. The disease affected several members of the royal families of Europe (figure 5.5).

King George III ruled England during the American Revolution. At age 50, he first experienced abdominal pain and constipation, followed by weak limbs, fever, a fast pulse, hoarseness, and dark red urine. Next, nervous system signs and symptoms began, including insomnia, headaches, visual problems, restlessness, delirium, convulsions, and stupor. His confused and racing thoughts, combined with actions such as ripping off his wig and running about naked while at the peak of a fever, convinced court observers that the king was mad. Just as Parliament was debating his ability to rule, he recovered.

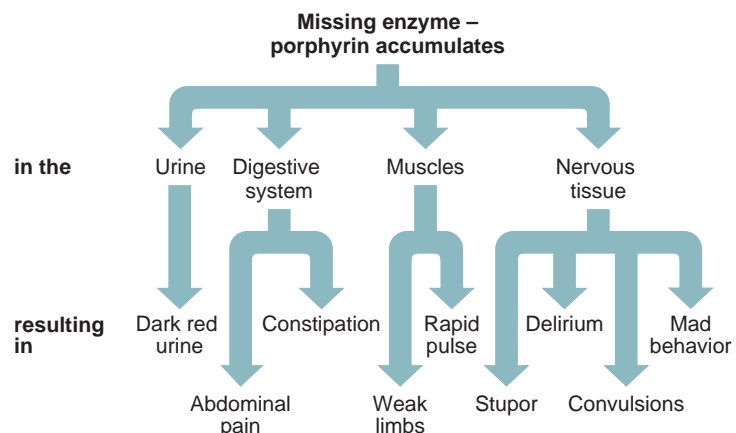
But the king's ordeal was far from over. He relapsed thirteen years later, then again three years after that. Always the symptoms appeared in the same order, beginning with

abdominal pain, fever, and weakness, and progressing to nervous system symptoms. Finally, an attack in 1811 placed George in a prolonged stupor, and the Prince of Wales dethroned him. George III lived for several more years, experiencing further episodes.

In George III's time, doctors were permitted to do very little to the royal body, and their diagnoses were based on what the king told them. Twentieth-century researchers found that porphyria variegata caused George's red urine. It is one of several types of porphyrias, which result from deficiency of any of several enzymes required to manufacture heme. Heme is part of hemoglobin, the molecule that carries oxygen in the blood and imparts the red color (figure 5.6). In the disease, a part of heme called a porphyrin ring is routed into the urine instead of being broken down and metabolized in cells. Porphyrin also builds up and attacks the nervous system.

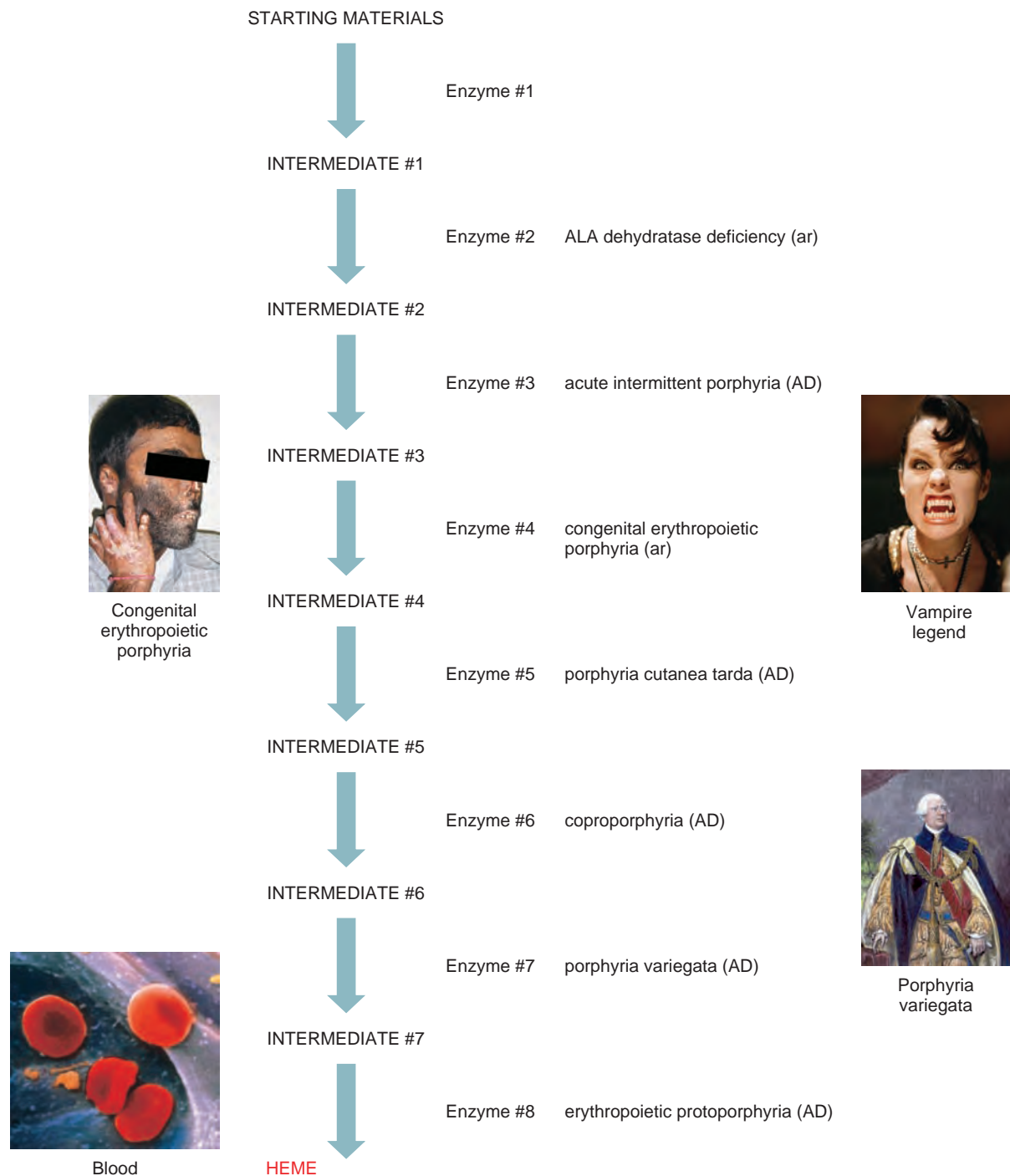
Examination of physicians' reports on George's royal relatives showed that the disorder was thought to be several different illnesses. Today, porphyria variegata remains rare, and people who have it are often misdiagnosed with a seizure disorder. Unfortunately, some seizure medications and anesthetics worsen symptoms.

Ironically, King George III's genetic disease may have been exacerbated by an environmental factor. Medical records and hair analysis indicate that a medicine based on the element antimony was forced upon the king in the madhouse. Antimony was



**Figure 5.5 Pleiotropy.** King George III suffered from the autosomal dominant disorder porphyria variegata—and so did several other family members. Because of pleiotropy, the family's varied illnesses and quirks appeared to be different, unrelated disorders. Symptoms appear every few years in a particular order.





**Figure 5.6 The porphyrias.** Errors in the heme biosynthetic pathway cause seven related, yet distinct, diseases. In each disorder, the intermediate biochemical that a deficient enzyme would normally affect builds up. The excess is excreted in the urine or accumulates in blood, feces, or inside red blood cells, causing symptoms (Table 5.2). People with various porphyria-related symptoms may have inspired the vampire and werewolf legends, including reddish teeth, pink urine, excess hair, and photosensitivity (avoidance of daylight).

often contaminated with arsenic, and arsenic inactivates several of the enzymes in the heme biosynthetic pathway! **Table 5.2** lists the symptoms of the porphyrias.

On a molecular level, pleiotropy occurs when a single protein affects different body parts or participates in more than one biochemical reaction. Consider Marfan

syndrome. The most common form of this autosomal dominant condition is a defect in an elastic connective tissue protein called fibrillin. The protein is

Table 5.2

## The Porphyrrias

Porphyria (OMIM)	Symptoms
ALA dehydratase deficiency (125270)	Abdominal pain, constipation, weakness, fever, rapid pulse, hoarseness, red urine, insomnia, headache, visual problems, delirium, “mad” behavior, stupor
Acute intermittent porphyria (1760000)	same as above
Coproporphria (121300)	same as above
Porphyria variegata (176200)	same as above
Congenital erythropoietic porphyria (263700)	Reddish teeth, pink urine, excess hair, photosensitivity
Porphyria cutanea tarda (176100)	Fragile, scarred, bleeding skin; pigment near eyes, excess hair, liver abnormalities
Erythropoietic protoporphyria (177000)	Photosensitivity; thick, waxy, itchy skin lesions

abundant in the lens of the eye, in the aorta (the largest artery in the body, leading from the heart), and in the bones of the limbs, fingers, and ribs. The symptoms are lens dislocation, long limbs, spindly fingers, and a caved-in chest. The most serious symptom is a life-threatening weakening in the aorta, which can suddenly burst. If the weakening is detected early, a synthetic graft can replace the section of artery wall.

Pleiotropy can be confusing even to medical doctors. *The New England Journal of Medicine* ran a contest to see if its physician readers could identify the cause of three symptoms of alkaptonuria, discussed in the chapter opening essay. Many couldn't.

## Genetic Heterogeneity

When different genes produce the same phenotype, a phenomenon called **genetic heterogeneity**, it may appear that Mendel's laws are not operating. For example, 132 forms of hearing loss are transmitted as autosomal recessive traits. If a man who is homozygous for a hearing loss gene on one chromosome has a child with a woman who is homozygous for another hearing loss gene on a different chromosome, then the child would not be deaf, because he or she would be heterozygous for both hearing-related genes. The different forms of hearing loss reflect the many ways that this sense can be genetically impaired.

Discovering additional genes that can cause a known disorder can have practical repercussions. This is the case for osteogenesis imperfecta, in which abnormal collagen causes children's bones to break easily (see figure 3.22). Often when a child is brought to the hospital and past fractures are discovered, child abuse is considered. A test for osteogenesis imperfecta can rule this out. However, some parents who insisted there was no abuse did not have the common mutation. In 2006, researchers discovered a rare mutation in a different gene, one that encodes an enzyme that adds a small chemical group to collagen, enabling it to function. A test for this mutation exonerated some parents accused of child abuse.

Genetic heterogeneity can occur when genes encode enzymes that catalyze the same biochemical pathway, or different proteins that are part of the pathway. This is also the case for some of the porphyrias described in table 5.2. For example, eleven biochemical reactions lead to blood clot formation. Mutations in genes that specify any of the enzymes that catalyze these reactions lead to several types of bleeding disorders.

## Phenocopies

An environmentally caused trait that appears to be inherited is a **phenocopy**. Such a trait can either produce symptoms

that resemble those of a known single-gene disorder or mimic inheritance patterns by affecting certain relatives. For example, the limb birth defect caused by the drug thalidomide, discussed in chapter 3, is a phenocopy of the inherited illness phocomelia. Physicians recognized the environmental disaster when they began seeing many children born with what looked like the very rare phocomelia. A birth defect caused by exposure to a teratogen was more likely than a sudden increase in incidence of a rare inherited disease.

A phenocopy of alkaptonuria occurred in some women with dark brown skin who used a bleaching cream that contained a chemical called hydroquinone. It caused darkening of the fingers and ears, just like alkaptonuria.

An infection can be a phenocopy. Children who have AIDS may have parents who also have the disease, but these children acquired AIDS by viral infection, not by inheriting a gene. A phenocopy caused by a highly contagious infection can seem to be inherited if it affects more than one family member.

Sometimes, common symptoms may resemble those of an inherited condition until medical tests rule heredity out. For example, an underweight child who has frequent colds may show some signs of cystic fibrosis, but may instead suffer from malnutrition. Negative test results for several common CF alleles would alert a physician to look for another cause.

## The Human Genome Sequence Adds Perspective

As researchers continue to identify and describe the genes sequenced in the human genome project, it is becoming clear that phenomena once considered to complicate single-gene inheritance aren't rare, and they may be common. As a result, terms such as *epistasis* and *genetic heterogeneity* are beginning to overlap and blur. Consider Marfan syndrome. Most affected individuals have a mutation in the fibrillin gene. However, some people with the syndrome instead have a mutation in the gene that encodes the transforming growth factor beta receptor (TGFB $\beta$ ) (OMIM 190181). Fibrillin and TGFB $\beta$  are

part of the same biochemical pathway. The conditions fit the definition of genetic heterogeneity because mutations in different genes cause identical symptoms. Yet they are also epistatic in the sense that a mutation in TGFBR blocks the activity of fibrillin.

Gene interactions also underlie penetrance and expressivity, once thought to be strictly a characteristic of a particular gene. Similarly, DNA microarrays that reveal gene expression patterns in different tissues are painting detailed portraits of pleiotropy—which, like epistasis, may not be unusual after all. That is, inherited disorders may affect more tissues or organs than we realize. Finally, more cases of genetic heterogeneity are being discovered as genes with redundant or overlapping functions are identified.

**Table 5.3** summarizes several of the phenomena that appear to alter single-gene inheritance. Perhaps our definitions and designations will change as improving technology enables us to describe and differentiate disorders in greater detail.

Gregor Mendel derived the two laws of inheritance working with traits conferred by genes located on different chromosomes in the nucleus. When genes do not conform to these conditions, however, the associated traits may not appear in Mendelian ratios.

The remainder of this chapter considers two types of gene transmission that do not fulfill the requirements for single-gene inheritance. One considers the role of chromosomes in trait transmission, and the other looks at information in mitochondrial DNA.

### Key Concepts

1. A lethal genotype does not appear as a progeny class.
2. In incomplete dominance, the heterozygote phenotype is intermediate between those of the homozygotes; in codominance, two different alleles for the same gene are each expressed.
3. In epistasis, one gene influences expression of another.
4. Genotypes vary in penetrance and expressivity of the phenotype.
5. A gene with more than one expression is pleiotropic.
6. Genetic heterogeneity occurs when different genes cause the same phenotype.
7. A trait caused by the environment but resembling a known genetic trait or occurring in certain family members is a phenocopy.
8. The human genome sequence reveals that several “exceptions” to Mendel’s laws are actually more common than was previously thought.

## 5.2 Maternal Inheritance and Mitochondrial Genes

The basis of the law of segregation is that both parents contribute genes equally to offspring. This is not the case for genes in mitochondria, the organelles that house the biochemical reactions that provide energy. Mitochondria in human cells contain several copies of a “mini-chromosome” that carries just 37 genes.

The inheritance patterns and mutation rates for mitochondrial genes differ from those for genes in the nucleus. Mitochondrial genes are maternally inherited. They are passed only from an individual’s mother because sperm almost never contribute mitochondria when they fertilize an oocyte. In the rare instances when mitochondria from sperm enter an oocyte, they are usually selectively destroyed early in development. Pedigrees that follow mitochondrial genes show a woman passing the trait to all her children, while a male cannot pass the trait to any of his (**figure 5.7**).

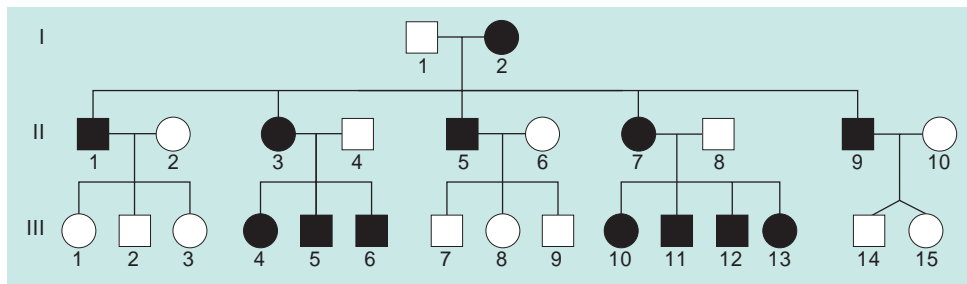
DNA in the mitochondria differs functionally from DNA in the nucleus in several ways (**table 5.4** and **figure 5.8**). MtDNA-encoded genes act in the mitochondrion, but the organelle also requires the activities of certain genes from the nucleus.

**Table 5.3**

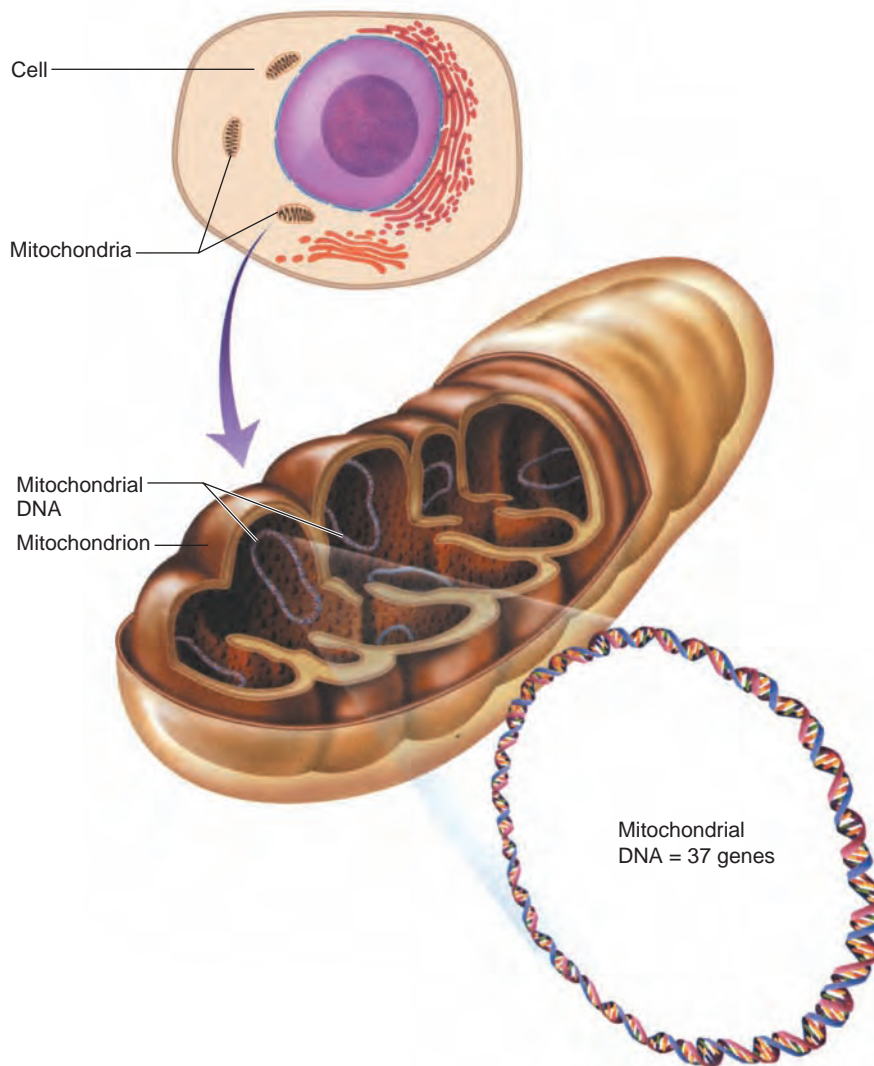
**Factors That Alter Single-Gene Phenotypic Ratios**

Phenomenon	Effect on Phenotype	Example
Lethal alleles	A phenotypic class does not survive to reproduce.	Spontaneous abortion
Multiple alleles	Many variants or degrees of a phenotype occur.	Cystic fibrosis
Incomplete dominance	A heterozygote’s phenotype is intermediate between those of two homozygotes.	Familial hypercholesterolemia
Codominance	A heterozygote’s phenotype is distinct from and not intermediate between those of the two homozygotes.	ABO blood types
Epistasis	One gene masks or otherwise affects another’s phenotype.	Bombay phenotype
Penetrance	Some individuals with a particular genotype do not have the associated phenotype.	Polydactyly
Expressivity	A genotype is associated with a phenotype of varying intensity.	Polydactyly
Pleiotropy	The phenotype includes many symptoms, with different subsets in different individuals.	Porphyria variegata
Phenocopy	An environmentally caused condition has symptoms and a recurrence pattern similar to those of a known inherited trait.	Infection
Genetic heterogeneity	Different genotypes are associated with the same phenotype.	Hearing impairment





**Figure 5.7 Inheritance of mitochondrial genes.** Mothers pass mitochondrial genes to all offspring. Fathers do not transmit mitochondrial genes because sperm only very rarely contribute mitochondria to fertilized ova.



**Figure 5.8 Mitochondrial DNA.** A mitochondrion contains several rings of DNA. Different alleles can reside on different copies of the mitochondrial chromosome.

Mitochondrial DNA does not cross over, and it mutates faster than DNA in the nucleus because it has fewer ways to repair DNA (discussed in chapter 12). The mitochondrion is

the site of the energy reactions that produce oxygen free radicals that damage DNA. Also unlike nuclear DNA, mtDNA is not wrapped in proteins, nor are genes “interrupted”

**Table 5.4**

### Features of Mitochondrial DNA

No crossing over
Fewer types of DNA repair
Inherited from the mother only
Many copies per mitochondrion and per cell
High exposure to oxygen free radicals
No histones (DNA-associated proteins)
No introns

by DNA sequences called introns that do not encode protein. Finally, a cell has one nucleus but many mitochondria—and each mitochondrion harbors several copies of its chromosome. Mitochondria with different alleles for the same gene can reside in the same cell.

### Mitochondrial Disorders

Mitochondrial genes encode proteins that participate in protein synthesis and energy production. Twenty-four of the 37 genes encode RNA molecules (22 transfer RNAs and 2 ribosomal RNAs) that help assemble proteins. The other 13 mitochondrial genes encode proteins that function in cellular respiration. These are the biochemical reactions that use energy from digested nutrients to synthesize ATP, the biological energy molecule.

In diseases resulting from mutations in mitochondrial genes, symptoms arise from tissues whose cells have many mitochondria, such as skeletal muscle. It isn’t surprising that a major symptom is often great fatigue. Inherited illnesses called mitochondrial myopathies produce weak and flaccid muscles and intolerance to exercise. Skeletal muscle fibers appear “red and ragged” when stained and viewed under a light microscope, their abundant abnormal mitochondria visible beneath the plasma membrane. Mitochondrial disorders may be more common than has been thought.

A defect in an energy-related gene can produce symptoms other than fatigue. This is the case for Leber optic atrophy (OMIM 535000), which impairs vision. First described in 1871 and its maternal transmission noted, this disorder was associated with a mitochondrial mutation that impairs

cellular energy reactions in 1988. Symptoms usually begin in early adulthood with a loss of central vision. Eyesight worsens and color vision vanishes as the central portion of the optic nerve degenerates.

A mutation in a mitochondrial gene that encodes a tRNA or rRNA can be devastating because it impairs the organelle's ability to manufacture proteins. Consider what happened to Linda S., a once active and articulate dental hygienist and travel agent. In her forties, Linda gradually began to slow down at work. She heard a buzzing in her ears and developed difficulty talking and walking. Then her memory began to fade in and out, she became lost easily in familiar places, and her conversation made no sense. Her condition worsened, and she developed diabetes, seizures, and pneumonia and became deaf and demented. She was finally diagnosed with MELAS, which stands for "mitochondrial myopathy encephalopathy lactic acidosis syndrome" (OMIM 540000). Linda died. Her son and daughter will likely develop the condition because they inherited her mitochondria.

A new technique called ooplasmic transfer can enable a woman to avoid transmitting a mitochondrial disorder. Mitochondria from a healthy woman's oocyte are injected into the oocyte of a woman who has a mitochondrial disorder. Then, the bolstered oocyte is fertilized in a laboratory dish by the partner's sperm, and the zygote is implanted in her uterus. Several dozen children, apparently free of mitochondrial disease, have been born from this technique.

## Heteroplasmy

The fact that a cell contains many mitochondria makes possible a rare condition called **heteroplasmy**. In this state a particular mutation is in some mitochondrial chromosomes, but not others. At each cell division, the mitochondria are distributed at random into daughter cells. Over time, the chromosomes within a mitochondrion tend to be all wild type or all mutant for any particular gene (a condition called homoplasmy). But different mitochondria can have different alleles predominating—and a cell has hundreds or thousands of mitochondria.

Heteroplasmy has several consequences for the inheritance of mitochondrial

phenotypes. Expressivity may vary widely among siblings, depending upon how many mutation-bearing mitochondria were in the oocyte that became each brother or sister. Severity of symptoms reflects which tissues have cells whose mitochondria bear the mutation. This is the case for a family with Leigh syndrome (OMIM 256000), which affects the enzyme that directly produces ATP. Two boys died of the severe form of the disorder because the brain regions that control movement rapidly degenerated. Another sibling was blind and had central nervous system degeneration. Several relatives, however, suffered only mild impairment of their peripheral vision. The more severely affected family members had more brain cells that received the mutation-bearing mitochondria.

The most severe mitochondrial illnesses are heteroplasmic. This is presumably because homoplasmy—when all mitochondria bear the mutant allele—too severely impairs protein synthesis or energy production for embryonic development to complete. Often, severe heteroplasmic mitochondrial disorders do not produce symptoms until adulthood because it takes many cell divisions, and therefore years, for a cell to receive enough mitochondria bearing mutant alleles to cause symptoms. For this reason, Leber optic atrophy usually does not affect vision until adulthood. Reading 9.1 relates how investigators used detection of heteroplasmy to solve a famous crime.

## Mitochondrial DNA Reveals the Past

Interest in mtDNA extends beyond the medical. MtDNA provides a powerful forensic tool used to link suspects to crimes, identify war dead, and support or challenge historical records. For example, sequencing mtDNA identified the son of Marie Antoinette and Louis XVI, who supposedly died in prison at age 10. In 1845, the boy was given a royal burial, but some people thought the buried child was an imposter. The boy's heart had been stolen at the autopsy, and through a series of bizarre events, wound up, dried out, in the possession of the royal family. Recently, researchers compared mtDNA sequences from cells in the boy's heart to corresponding sequences in heart and hair cells from Marie

Antoinette (her decapitated body identified by her fancy underwear), two of her sisters, and living relatives Queen Anne of Romania and her brother. The genetic evidence showed that the unfortunate boy was indeed the prince, Louis XVII.

## Key Concepts

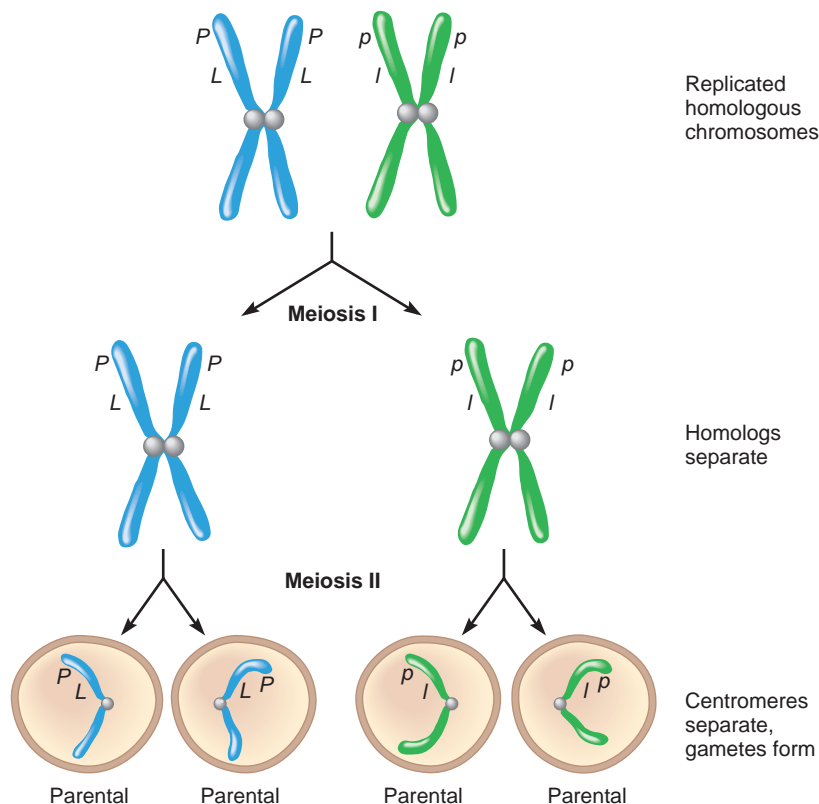
1. Mitochondrial genes are maternally inherited and mutate rapidly. A cell contains many mitochondria, which have many copies of the mitochondrial genome.
2. Mitochondrial genes encode RNAs or proteins that function in protein synthesis or energy metabolism.
3. In heteroplasmy, cells contain mitochondria that have different alleles of a gene.

## 5.3 Linkage

Most of the traits that Mendel studied in pea plants were conferred by genes on different chromosomes. When genes are located close to each other on the same chromosome, they usually do not segregate at random during meiosis and therefore do not support Mendel's predictions. Instead, they are packaged into the same gametes and are said to be "linked" (**figure 5.9**). **Linkage** refers to the transmission of genes on the same chromosome. Linked genes do *not* assort independently and do *not* produce Mendelian ratios for crosses tracking two or more genes. Understanding and using linkage as a mapping tool has been critical in identifying disease-causing genes, and helped pave the way for sequencing genomes.

## Discovery in Pea Plants

William Bateson and R. C. Punnett first observed the unexpected ratios indicating linkage in the early 1900s, again in pea plants. They crossed true-breeding plants with purple flowers and long pollen grains (genotype *PPLL*) to true-breeding plants with red flowers and round pollen grains (genotype *ppll*). The plants in the next generation, of genotype *PpLl*, were then self-crossed. But this dihybrid cross did not yield



**Figure 5.9 Inheritance of linked genes.** Genes linked closely to one another on the same chromosome are usually inherited together when that chromosome is packaged into a gamete.

the expected 9:3:3:1 phenotypic ratio that Mendel's second law predicts (**figure 5.10**).

Bateson and Punnett noticed that two types of third-generation peas, those with the parental phenotypes  $P\_L\_$  and  $ppll$ , were more abundant than predicted, while the other two progeny classes,  $ppL\_$  and  $P\_ll$ , were less common (the blank indicates that the allele can be dominant or recessive). The more prevalent parental allele combinations, Bateson and Punnett hypothesized, could reflect genes that are transmitted on the same chromosome and that therefore do not separate during meiosis. The two less common offspring classes could also be explained by a meiotic event—crossing over. Recall that this is an exchange between homologs that mixes up maternal and paternal gene combinations without disturbing the sequence of genes on the chromosome (**figure 5.11**).

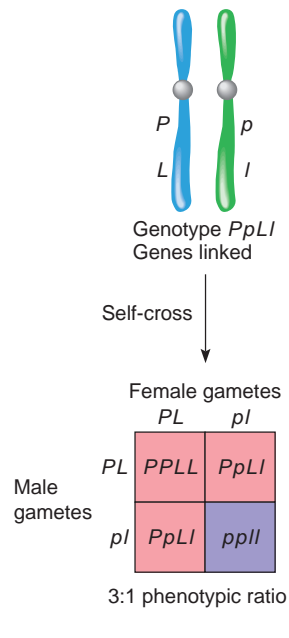
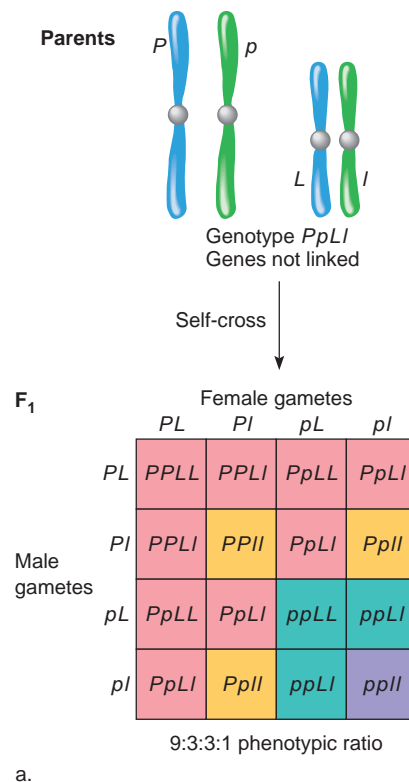
Progeny that exhibit this mixing of maternal and paternal alleles on a single chromosome are called **recombinant**. *Parental* and *recombinant* are relative terms. Had the parents in Bateson and Punnett's

crosses been of genotypes  $ppL\_$  and  $P\_ll$ , then  $P\_L\_$  and  $ppll$  would be recombinant rather than parental classes.

Two other terms describe the configurations of linked genes in dihybrids. Consider a pea plant with genotype  $PpLl$ . These alleles can be part of the chromosomes in either of two ways. If the two dominant alleles are on one chromosome and the two recessive alleles on the other, the genes are in "*cis*." In the opposite configuration, with one dominant and one recessive allele on each chromosome, the genes are in "*trans*" (**figure 5.12**). Whether alleles in a dihybrid are in *cis* or *trans* is important in distinguishing recombinant from parental progeny classes in specific crosses.

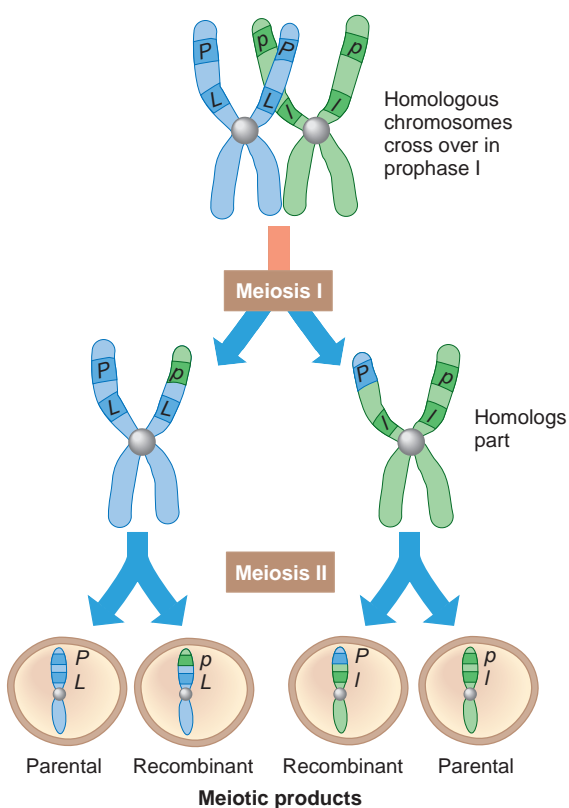
## Linkage Maps

As Bateson and Punnett were discovering linkage in peas, geneticist Thomas Hunt Morgan and his coworkers at Columbia University were doing the same using the fruit fly *Drosophila melanogaster*. They assigned genes to relative positions on



**Figure 5.10 Expected results of a dihybrid cross.** (a) When genes are not linked, they assort independently. The gametes then represent all possible allele combinations. The expected phenotypic ratio of a dihybrid cross is 9:3:3:1. (b) If genes are linked on the same chromosome, only two allele combinations are expected in the gametes. The phenotypic ratio is 3:1, the same as for a monohybrid cross.



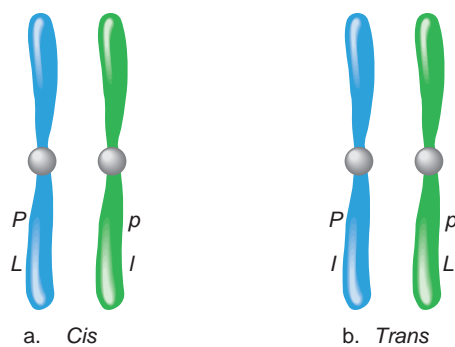


**Figure 5.11 Crossing over disrupts linkage.** The linkage between two genes may be interrupted if the chromosome they are on crosses over with its homolog between the two genes. Crossing over packages recombinant groupings of the genes into gametes.

chromosomes and compared progeny class sizes to assess whether traits were linked. They soon realized that the pairs of traits fell into four groups. Within each group, crossed dihybrids did not produce offspring classes according to Mendel's second law. Plus, the number of linkage groups—four—matched the number of chromosome pairs in the fly. Coincidence? No. The traits fell into four groups because their genes are inherited together on the same chromosome.

The genius of the work on linkage in fruit flies was that the researchers translated their data into actual maps depicting positions of genes on chromosomes. Morgan wondered why the sizes of the recombinant classes varied for different genes. In 1911, Morgan's undergraduate student, Alfred Sturtevant, proposed that the farther apart two genes are on a chromosome, the more likely they are to cross over simply because more physical distance separates them (**figure 5.13**).

The correlation between crossover frequency and the distance between genes is used to construct **linkage maps**. These diagrams show the order of genes on chromosomes and the relative distances between



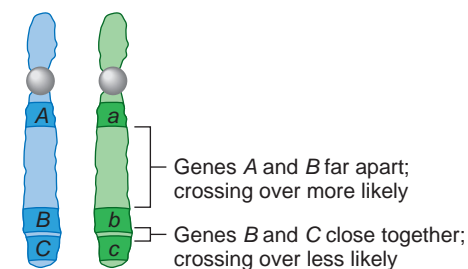
P = Purple flowers  
p = Red flowers  
L = Long pollen grains  
l = Round pollen grains

**Figure 5.12 Allele configuration is important.** Parental chromosomes can be distinguished from recombinant chromosomes only if the allele configuration of the two genes is known—they are either in *cis* (**a**) or in *trans* (**b**).

them. The distance is represented using “map units” called centimorgans, where 1 centimorgan equals 1 percent recombination. The frequency of a crossover between any two linked genes is inferred from the proportion of offspring that are recombinant. Frequency of recombination is based on the percentage of meiotic divisions that break the linkage between—that is, separate—two parental alleles. Genes at opposite ends of the same chromosome often cross over, generating a large recombinant class. Genes lying very close on the chromosome would only rarely be separated by a crossover. The probability that linked genes that are as far apart as possible on a chromosome will recombine due to crossing over approaches the probability that, if on different chromosomes, they would independently assort—about 50 percent. **Figure 5.14** illustrates this distinction.

The situation with linked genes can be compared to a street lined with stores on both sides. There are more places to cross the street between stores at opposite ends than between two stores in the middle of the block. Similarly, more crossovers, or progeny with recombinant genotypes, are seen when two genes are farther apart on the same chromosome.

As the twentieth century progressed, geneticists in Columbia University's “fly room” mapped several genes on all four chromosomes, and in other labs many genes



**Figure 5.13 Breaking linkage.**

Crossing over is more likely to occur between the widely spaced linked genes A and B, or between A and C, than between the more closely spaced linked genes B and C, because there is more room for an exchange to occur.

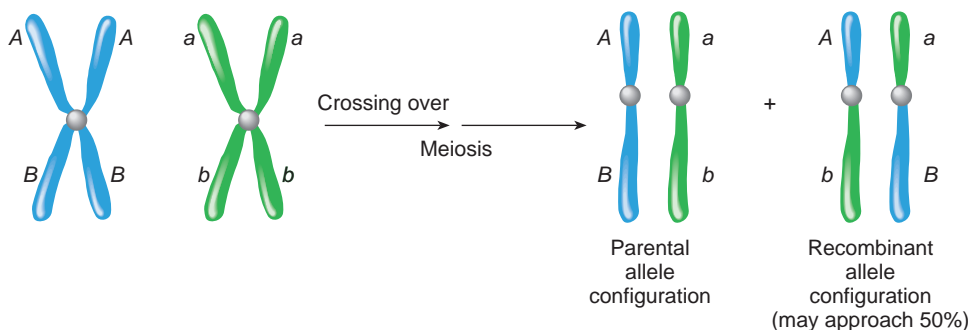
were assigned to the human X chromosome. Localizing genes on the X chromosome was easier than doing so on the autosomes, because X-linked traits follow an inheritance pattern that is distinct from the one followed by all autosomal genes. In human males, with their single X chromosome, recessive alleles on the X are expressed. We return to this point in chapter 6.

By 1950, geneticists began to think about mapping genes on the 22 human autosomes. To start, a gene must be matched to its chromosome. This became possible, rarely, when people with a particular inherited condition or trait also had a specific chromosome abnormality. Matching phenotypes to chromosomal variants, a field called cytogenetics, is the subject of chapter 13.

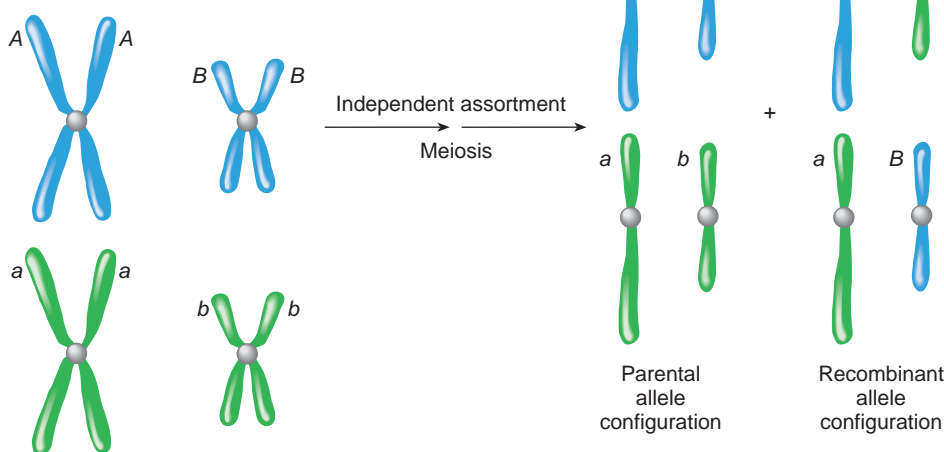
In 1968, researchers assigned the first human gene to an autosome. R. P. Donohue was observing chromosomes in his own white blood cells when he noticed a dark area consistently located near the centromere of one member of his largest chromosome pair (chromosome 1). He then examined chromosomes from several family members for the dark area, noting also whether each family member had a blood type called Duffy. (Recall that blood types refer to the patterns of sugars on red blood cell surfaces.) Donohue found that the Duffy blood type was linked to the chromosome variant. He could predict a relative's Duffy blood type by whether or not the chromosome had the telltale dark area.

Finding a chromosomal variation and using it to detect linkage to another gene was a valuable but rare achievement. More often, researchers used the sorts of experiments Sturtevant conducted on his

### Linked Genes



### Nonlinked Genes



**Figure 5.14 Linkage versus nonlinkage (independent assortment).** When two genes are widely separated on a chromosome, the likelihood of a crossover is so great that the recombinant class may approach 50 percent—which may appear to be the result of independent assortment.

flies—calculating percent recombination (crossovers) between two genes whose locations on the chromosome were known. However, because humans do not have hundreds of offspring, as fruit flies do, nor do they produce a new generation every 10 days, obtaining sufficient data to establish linkage relationships requires observing the same traits in many families and pooling the information. Today, even though we know the human genome sequence, linkage remains a powerful tool to track disease-associated genes.

### Solving a Problem: Linkage

As an example of determining the degree of linkage by percent recombination, consider the traits of Rh blood type and a form of anemia called elliptocytosis

(OMIM 111700) (OMIM 130500). An Rh<sup>+</sup> phenotype corresponds to genotypes RR or Rr. (This is simplified.) The anemia corresponds to genotypes EE or Ee.

Suppose that in 100 one-child families, one parent is Rh negative with no anemia (rree), and the other parent is Rh positive with anemia (RrEe), and the R and E (or r and e) alleles are in *cis*. Of the 100 offspring, 96 have parental genotypes (re/re or RE/re) and four individuals are recombinants for these two genes (Re/re or rE/re). Percent recombination is therefore 4 percent, and the two linked genes are 4 centimorgans apart.

Consider another pair of linked genes in humans. Nail-patella syndrome (OMIM 161200) is a rare autosomal dominant trait that causes absent or underdeveloped fingernails and toenails, and painful

arthritis in the knee and elbow joints. The gene is 10 map units from the *I* gene that determines the ABO blood type, on chromosome 9. Geneticists determined the map distance by pooling information from many families. The information can be used to predict genotypes and phenotypes in offspring, as in the following example.

Greg and Susan each have nail-patella syndrome. Greg has type A blood, and Susan has type B blood. They want to know the chance that a child of theirs would inherit normal nails and knees and type O blood. Because information is available on Greg and Susan's parents, a genetic counselor can deduce their allele configurations (figure 5.15).

Greg's mother has nail-patella syndrome and type A blood. His father has normal nails and type O blood. Therefore, Greg must have inherited the dominant nail-patella syndrome allele (*N*) and the *I*<sup>A</sup> allele from his mother, on the same chromosome. We know this because Greg has type A blood and his father has type O blood—therefore, he couldn't have gotten the *I*<sup>A</sup> allele from his father. Greg's other chromosome 9 must carry the alleles *n* and *i*. His alleles are therefore in *cis*.

Susan's mother has nail-patella syndrome and type O blood, and so Susan inherited *N* and *i* on the same chromosome. Because her father has normal nails and type B blood, her homolog bears alleles *n* and *I*<sup>B</sup>. Her alleles are in *trans*.

Determining the probability that their child could have normal nails and knees and type O blood is the easiest question the couple could ask. The only way this genotype can arise from theirs is if an *ni* sperm (which occurs with a frequency of 45 percent, based on pooled data) fertilizes an *ni* oocyte (which occurs 5 percent of the time). The result—according to the product rule—is a 2.25 percent chance of producing a child with the *nnii* genotype.

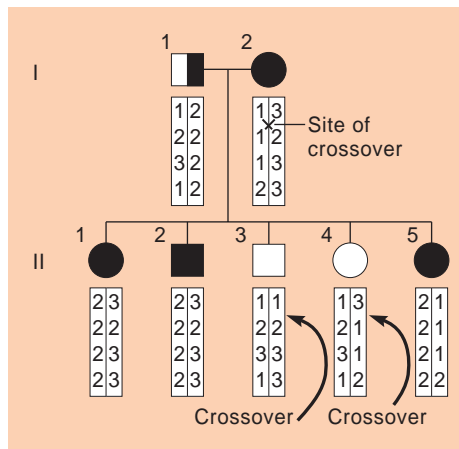
Calculating other genotypes for their offspring is more complicated, because more combinations of sperm and oocytes could account for them. For example, a child with nail-patella syndrome and type AB blood could arise from all combinations that include *I*<sup>A</sup> and *I*<sup>B</sup> as well as at least one *N* allele (assuming that the *NN* genotype has the same phenotype as the *Nn* genotype).





Haplotypes can look complicated, because markers are often given names that have meaning only to their discoverers. They read like license plates, bearing labels such as D9S1604. The haplotypes in the pedigree in **figure 5.17**, for a family with cystic fibrosis, are simplified. Each set of numbers beneath a symbol represents a “license plate” haplotype. Haplotypes make it possible to track which parent transmits which genes and chromosomes to offspring. In figure 5.17, knowing the haplotype of individual II–2 reveals which chromosome in parent I–1 contributes the mutant allele. Because Mr. II–2 received haplotype 3233 from his affected mother, his other haplotype, 2222, comes from his father. Since Mr. II–2 is affected and his father is not, the father must be a heterozygote, and 2222 must be the haplotype linked to the mutant CFTR allele.

It has been exciting to watch gene mapping evolve from the initial associations between blood types and chromosomal quirks, to today’s maps with their millions of signposts along the sequenced human genome. Throughout the 1990s, each October, *Science* magazine published a human genome map. The number of identified genes steadily



**Figure 5.17 Haplotypes.** The numbers in bars beneath pedigree symbols enable researchers to track specific chromosome segments with markers. Disruptions of a marker sequence indicate crossover sites.

grew as chromosome depictions became ever more packed with information. From that information, during your lifetime, will spring a revolution in understanding our genetic selves.

## Key Concepts

1. Genes on the same chromosome are linked, and they are inherited in patterns that differ from the patterns of the unlinked genes Mendel studied.
2. Crosses involving linked genes produce a large parental class and a small recombinant class (caused by crossing over).
3. The farther apart two genes are on a chromosome, the more likely they are to cross over. Linkage maps translate crossover frequency into relative distances between genes on a chromosome.
4. Cytogenetic abnormalities revealed the first linkage associations.
5. Linkage disequilibrium is a linkage combination that is stronger than that predicted by gene frequencies in a population.
6. Linkage maps reflect the percent recombination between linked genes. LOD scores describe the tightness of linkage and thereby the proximity of a gene to a marker. Haplotypes indicate linked DNA sequences.

## Summary

### 5.1 When Gene Expression Appears to Alter Mendelian Ratios

1. Homozygosity for lethal recessive alleles stops development before birth, eliminating an offspring class.
2. A gene can have multiple alleles because its sequence can be altered in many ways. Different allele combinations may produce different variations of the phenotype.
3. Heterozygotes of **incompletely dominant** alleles have phenotypes intermediate between those associated with the two homozygotes. **Codominant** alleles are both expressed in the phenotype.
4. In **epistasis**, one gene affects the phenotype of another.
5. An incompletely **penetrant** genotype is not expressed in all individuals who inherit it. Phenotypes that vary in intensity among individuals are variable in **expressivity**.
6. **Pleiotropic** genes have several expressions.

7. In **genetic heterogeneity**, two or more genes specify the same phenotype.
8. A **phenocopy** is a characteristic that appears to be inherited but is environmentally caused.
9. The human genome sequence is explaining seeming exceptions to Mendel’s laws.

### 5.2 Maternal Inheritance and Mitochondrial Genes

10. Only females transmit mitochondrial genes; males can inherit such a trait but cannot pass it on.
11. Mitochondrial genes do not cross over, and they mutate more frequently than nuclear DNA.
12. The 37 mitochondrial genes encode tRNA, rRNA, or proteins involved in protein synthesis or energy reactions.
13. Many mitochondrial disorders are **heteroplasmic**, with mitochondria in a single cell harboring different alleles.

### 5.3 Linkage

14. Genes on the same chromosome are **linked** and, unlike genes that independently assort, produce many individuals with parental genotypes and a few with **recombinant** genotypes.
15. **Linkage maps** depict linked genes. Researchers can examine a group of known linked DNA sequences (a **haplotype**) to follow the inheritance of certain chromosomes.
16. Knowing whether linked alleles are in *cis* or *trans*, and using crossover frequencies from pooled data, one can predict the probabilities that certain genotypes will appear in progeny.
17. Genetic linkage maps assign distances to linked genes based on crossover frequencies.

# Review Questions

1. Explain how each of the following phenomena can disrupt Mendelian phenotypic ratios.
  - a. lethal alleles
  - b. multiple alleles
  - c. incomplete dominance
  - d. codominance
  - e. epistasis
  - f. incomplete penetrance
  - g. variable expressivity
  - h. pleiotropy
  - i. a phenocopy
  - j. genetic heterogeneity
2. How does the relationship between dominant and recessive alleles of a gene differ from epistasis?
3. Why can transmission of an autosomal dominant trait with incomplete penetrance look like autosomal recessive inheritance?
4. How does inheritance of ABO blood type exhibit both complete dominance and codominance?
5. How could two people with albinism have a child who has normal skin pigment?
6. How do the porphyrias exhibit variable expressivity, pleiotropy and genetic heterogeneity?
7. The lung condition emphysema may be caused by lack of an enzyme, or by smoking. Which cause is a phenocopy?
8. List three ways that mtDNA differs from DNA in a cell's nucleus.
9. Describe why inheritance of mitochondrial DNA and linkage are exceptions to Mendel's laws.
10. How does a pedigree for a maternally inherited trait differ from one for an autosomal dominant trait?
11. If researchers could study pairs of human genes as easily as they can study pairs of genes in fruit flies, how many linkage groups would they detect?

# Applied Questions

1. For each of the diseases described in situations *a* through *i*, indicate which of the following phenomena (A–H) is at work. More than one may apply.
  - A. lethal alleles
  - B. multiple alleles
  - C. epistasis
  - D. incomplete penetrance
  - E. variable expressivity
  - F. pleiotropy
  - G. a phenocopy
  - H. genetic heterogeneity
  - a. A woman has severe neurofibromatosis type 1. She has brown spots on her skin and several large tumors beneath her skin. A genetic test shows that her son has inherited the disease-causing autosomal dominant allele, but he has no symptoms.
  - b. A man would have a widow's peak, if he wasn't bald
  - c. A man and woman have six children. They also had two stillbirths—fetuses that died shortly before birth.
  - d. Most children with cystic fibrosis have frequent lung infections and digestive difficulties. Some people have mild cases, with onset of minor respiratory problems in adulthood. For some men with CF, their only symptom is infertility.
  - e. Long QT syndrome, which causes an abnormal heartbeat, may be caused by mutation in the gene encoding a potassium channel protein or a mutation in the gene encoding an ankyrin protein.
  - f. In Labrador retrievers, the *B* allele confers black coat color and the *b* allele brown coat color. The *E* gene controls the expression of the *B* gene. If a dog inherits the *E* allele, the coat is golden no matter what the *B* genotype is. A dog of genotype *ee* expresses the *B* (black) phenotype.
  - g. Two parents are heterozygous for genes that cause albinism, but each gene specifies a different enzyme in the biochemical pathway for skin pigment synthesis. Their children thus do not face a 25 percent risk of having albinism.
  - h. Alagille syndrome (OMIM 118450), in its most severe form, prevents the formation of ducts in the gallbladder, causing liver damage. Affected children also usually have heart murmurs, unusual faces, a line in the eye, and butterfly-shaped vertebrae. Such children often have one otherwise healthy parent who has a heart murmur, unusual face, and butterfly vertebrae.
  - i. Two young children in a family have terribly decayed teeth. Their parents think it is genetic, but the true cause is a babysitter who puts them to sleep with juice bottles in their mouths.
2. If many family studies for a particular autosomal recessive condition reveal fewer affected individuals than Mendel's law predicts, the explanation may be either incomplete penetrance or lethal alleles. How might you use haplotypes to determine which of these two possibilities is the cause?
3. A man who has type O blood has a child with a woman who has type A blood. The woman's mother has AB blood, and her father, type O. What is the probability that the child is of blood type
  - a. O
  - b. A
  - c. B
  - d. AB?
4. Two people who are heterozygous for familial hypercholesterolemia are concerned that a child might inherit the severe form of the illness. What is the probability that this will happen?
5. Enzymes are used in blood banks to remove the A and B antigens from blood types A and B. This makes the blood type O.
  - a. Does this alter the phenotype or the genotype?

- b. Removing the A and B antigens from red blood cells is a phenocopy of what genetic phenomenon?
6. Ataxia-oculomotor apraxia syndrome (OMIM 208920), which impairs the ability to feel and move the limbs, usually begins in early adulthood. The molecular basis of the disease is impairment of ATP production in mitochondria, but the mutant gene is in the nucleus of the cells. Would this disorder be inherited in a Mendelian fashion? Explain your answer.
  7. What is the chance that Greg and Susan, the couple with nail-patella syndrome, could have a child with normal nails and type AB blood?
  8. A gene called *secretor* (OMIM 182100) is located 1 map unit from the *H* gene that confers the Bombay phenotype on chromosome 19. *Secretor* is dominant, and a person of either genotype *SeSe* or *Sese* secretes the ABO and H blood type antigens in saliva and other body fluids. This secretion, which the person is unaware of, is the phenotype. A man has the Bombay phenotype and is not a secretor. A woman does not have the Bombay phenotype and is a secretor. She is a dihybrid whose alleles are in *cis*. What is the chance that their child will have the same genotype as the father?
  9. A Martian creature called a gazook has 17 chromosome pairs. On the largest chromosome are genes for three traits—round or square eyeballs (*R* or *r*); a hairy or smooth tail (*H* or *h*); and 9 or 11 toes (*T* or *t*). Round eyeballs, hairy tail, and 9 toes are dominant to square eyeballs, smooth tail, and 11 toes. A trihybrid male has offspring with a female who has square eyeballs, a smooth tail, and 11 toes on each of her three feet. She gives birth to 100 little gazooks, who have the following phenotypes:
    - 40 have round eyeballs, a hairy tail, and 9 toes
    - 40 have square eyeballs, a smooth tail, and 11 toes
    - 6 have round eyeballs, a hairy tail, and 11 toes
    - 6 have square eyeballs, a smooth tail, and 9 toes
    - 4 have round eyeballs, a smooth tail, and 11 toes
    - 4 have square eyeballs, a hairy tail, and 9 toes

- Draw the allele configurations of the parents.
- Identify the parental and recombinant progeny classes.
- What is the crossover frequency between the *R* and *T* genes?

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 5**, and **Web Activities** to find the website links needed to complete the following activities.

10. Go to the Family Village website. Family Village is a clearinghouse for disease information. Click on library. Explore the diseases, and identify one that exhibits pleiotropy.
11. Go to the United Mitochondrial Disease Foundation website and describe the phenotype of a mitochondrial disorder.
12. Browse the National Center for Biotechnology Information (NCBI) site, and list three sets of linked genes. Consult OMIM to describe the trait or disorder that each specifies.
13. Use OMIM to identify a genetically heterogeneous condition, and explain why this description applies.
14. For some of the porphyrias, attacks are precipitated by an environmental trigger. Using OMIM, describe factors that can trigger an attack of any of the following:
  - a. acute intermittent porphyria
  - b. porphyria cutanea tarda
  - c. coproporphyria
  - d. porphyria variegata
  - e. erythropoietic protoporphyria

### Case Studies and Research Results

15. Connie Winslow is deaf. When she was old enough to attend school, she began having fainting spells, especially when she became excited. When she fainted while opening Christmas gifts, her parents took her to the emergency room, where doctors assured them, as they had in the past, that there wasn't a problem. The spells continued, and Connie became able to predict the attacks, telling her parents that her head hurt beforehand. Her parents took her to a neurologist, who checked Connie's heart and diagnosed long-QT

syndrome with deafness, also known as Jervell and Lange-Nielsen syndrome (see OMIM 220400 and Reading 2.2). This is a severe form of inherited heartbeat irregularity that can be fatal. Seven different genes can cause long-QT syndrome. The doctor told them of a case described in a textbook from 1856: a young girl, called at school to face the headmaster for an infraction, became so agitated that she dropped dead. The parents were not surprised; they had lost two other children to great excitement.

The Winslows visited a medical geneticist, who discovered that each had a mild heartbeat irregularity that did not produce symptoms. Connie's parents had normal hearing. Connie's younger brother Jim was also hearing-impaired and suffered night terrors, but had so far not fainted during the day. Like Connie, he had the full syndrome. Tina, still a baby, was also tested. She did not have either form of the family's illness; her heartbeat was normal.

Today, Connie and Jim are treated with beta blocker drugs, and each has a pacemaker to regulate heartbeat. Connie may receive an implantable defibrillator to automatically correct her heartbeat when it veers out of control. Diagnosing her may have saved her brother's life.

- a. Which of the following applies to the condition in this family?
  - i. genetic heterogeneity
  - ii. pleiotropy
  - iii. variable expressivity
  - iv. incomplete dominance
  - v. a phenocopy
- b. How is the inheritance pattern of Jervell and Lange-Nielsen syndrome similar to that of familial hypercholesterolemia?
- c. How is it possible that Tina did not inherit either the serious or asymptomatic form of the illness?
- d. Do the treatments for the condition affect the genotype or the phenotype?
16. The definition of "recessive" may be changing, because of technology. In the past, recessive meant an allele that was not expressed in a heterozygote. However, researchers are now able to detect changes in the biochemistry of carriers that do not affect the phenotype. For example, Nijmegen breakage syndrome (NBS, OMIM 251260) is autosomal recessive and causes slow growth,



impaired immunity, and increased cancer risk. Carriers appear normal but may be more likely to develop cancer than those without a mutation. Researchers found that levels of proteins encoded by 16 other genes are different in carriers of NBS.

- a. How do these new findings complicate the traditional definition of recessive?
- b. Do you think there is any value in detecting carriers of NBS? If so, what is it?

17. Barnabas Collins has congenital erythropoietic porphyria, and his wife Angelique is a carrier of ALA dehydratase deficiency. What is the chance that if they have a child, he or she will have a porphyria?

## A Second Look

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1. Several mutations are known in the gene that encodes the enzyme that is deficient in alkaptonuria. How is this possible if a person only has two alleles?
2. Symptoms of alkaptonuria vary in the number of joints that turn black and become painful. Does this indicate incomplete penetrance or variable expressivity?
3. Explain the basis of the pleiotropy in alkaptonuria.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

Cohen syndrome  
Enamel hypoplasia  
Hair and eye color  
Thrombocytopenia and absent radius syndrome



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Matters of Sex

## CHAPTER CONTENTS

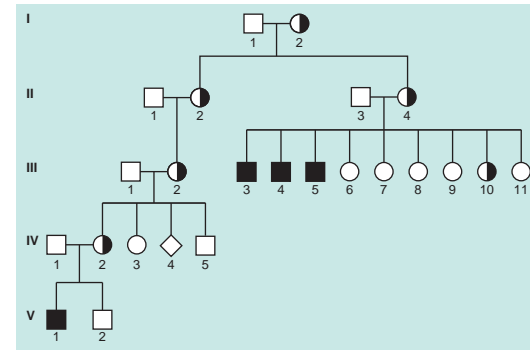
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## A FAMILY TRAGEDY AVERTED

In 1937, Alfred Wiskott, a pediatrician in Germany, encountered a family that had 6 healthy girls, but 3 boys who died of the same illness, at 4, 8, and 18 months. The boys had bruises and skin markings due to poor clotting, the skin condition eczema, bloody diarrhea, ear infections and pneumonia. All died from bleeding in their digestive tracts and infection in the blood. Dr. Wiskott noted the inherited nature of the condition and remarked that it seemed to affect only boys.

In 1954, another physician, Robert Aldrich, described the disorder in a large Dutch family. Sick boys who survived beyond childhood often developed blood-borne cancers or autoimmune disorders. The disease was named Wiskott-Aldrich syndrome (OMIM 301000), and it was used to pioneer bone marrow transplantation. Because several symptoms result from blood abnormalities, replacing the blood supply with a bone marrow transplant made sense.

In 2006, German researchers contacted living relatives of the original family that included the three sick little boys. Their pedigree is shown in the figure. Genetic tests revealed a mutation in the *WAS* gene in which two DNA bases are missing. Carrier females were identified, and an affected little boy, the first cousin twice removed of the three original boys, was successfully treated with a stem cell transplant from an unrelated donor.



In 1937, Alfred Wiskott described the family depicted in this pedigree. In the third generation, three baby boys were sick, but their six sisters were healthy. Two generations later, another little boy was born with the X-linked illness, now called Wiskott-Aldrich syndrome, but he was successfully treated with a stem cell transplant.

Whether we are male or female is enormously important in our lives, affecting our relationships, how we think and act, and how others perceive us. Gender is ultimately a genetic phenomenon, but it is also layered with psychological and sociological components.

Maleness or femaleness is determined at conception, when he inherits an X and a Y chromosome, or she inherits two X chromosomes. Another level of sexual identity comes from the control that hormones exert over the development of reproductive structures. Finally, both biological factors and social cues influence sexual feelings, including the strong sense of whether we are male or female.

## 6.1 Sexual Development

Gender differences do not become apparent until the ninth week of prenatal development. During the fifth week, all embryos develop two unspecialized gonads, which are organs that will develop as either testes or ovaries. Each such “indifferent” gonad forms near two sets of ducts that present two developmental options. If one set of tubes, called the Müllerian ducts, continues to develop, they eventually form the sexual structures characteristic of a female. If the other set, the Wolffian ducts, persist, male sexual structures form.

The choice to follow a male or female developmental pathway occurs during the sixth week, depending upon the sex chromosome constitution and actions of certain genes. If a gene on the Y chromosome called *SRY* (for “sex-determining region of the Y”) is activated, hormones steer development along a male route. In the absence of *SRY* activation, a female develops (figure 6.1).

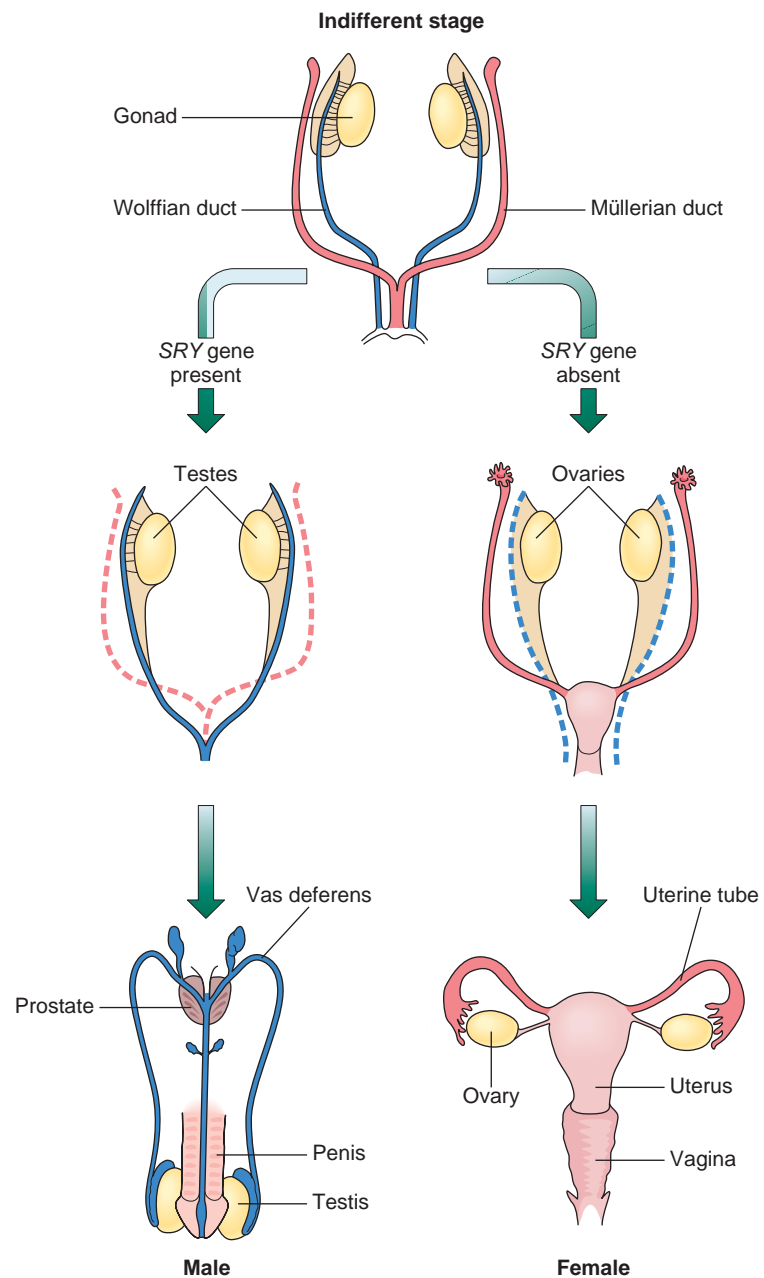
Femaleness was long considered a “default” option in human development, but sex determination is more accurately described as a fate imposed on ambiguous precursor structures. Several genes besides *SRY* guide early development of reproductive structures. A mutation in a gene called *Wnt4*, for example, causes a female to have high levels of male sex hormones and lack a vaginal canal and uterus. Hence, the gene

is essential for development and maturation as a female.

## Sex Chromosomes

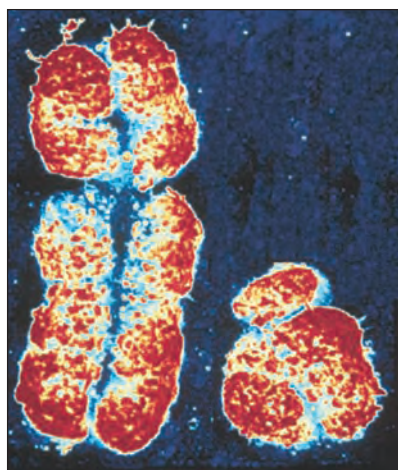
Human males and females have equal numbers of autosomes, but males have one X chromosome and one Y chromosome, and females have two X chromosomes

(figure 6.2). The sex with two different sex chromosomes is called the **heterogametic sex**, and the other, with two of the same sex chromosomes, is the **homogametic sex**. In humans, males are heterogametic and females are homogametic. Some other species are different. In birds and snakes, for example, males are ZZ (homogametic) and females are ZW (heterogametic).



**Figure 6.1 Male or female?** The paired duct systems in the early human embryo may develop into male or female reproductive organs. The red tubes represent female structures and the blue tubes, male structures.





X chromosome Y chromosome

### Figure 6.2 The X and Y chromosomes.

In humans, females are the homogametic sex (XX) and males are the heterogametic sex (XY). (The chromosomes are in the replicated form because they were dividing when photographed.)

The X chromosome in humans has more than 1,500 genes. The much smaller Y chromosome has 231 protein-encoding genes. In meiosis in a male, the X and Y chromosomes act as if they are a pair of homologs. We will introduce the Y chromosome here, then consider the X in section 6.2.

Identifying genes on the human Y chromosome has been extremely difficult. Before the human genome sequence became available, researchers inferred the functions and locations of Y-linked genes by examining men missing parts of the chromosome and determining how they differ from normal. Creating linkage maps, which was possible for the other chromosomes, didn't work for the Y because it does not have a homolog with which to cross over (although its tips can cross over with the X chromosome).

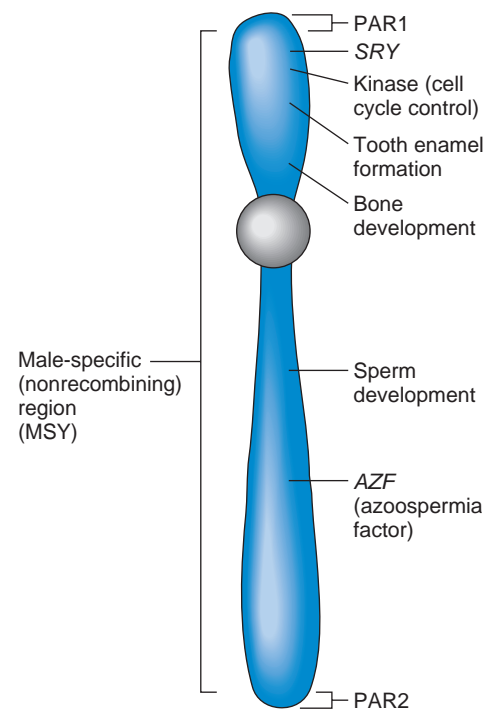
Analysis of the genome sequence has revealed one source of the difficulty in mapping the Y chromosome: It has a very unusual organization. In the 95 percent of the chromosome that harbors male-specific genes, many DNA segments are palindromes. In written languages, palindromes are sequences of letters that read the same in both directions—"Madam, I'm Adam," for example. This symmetry in a DNA sequence, described by researchers as "a hall of mirrors," destabilizes DNA replication.

As a result, during meiosis, sections of a Y chromosome attract each other. This can loop out parts in between, which may account for many cases of male infertility caused by missing parts of the Y. Yet this "hall of mirrors" organization may also provide a way for the chromosome to recombine with itself, essentially sustaining its structure. Two researchers—one an XX, one an XY—take a lighthearted look at the curious structure of the human Y chromosome in "In Their Own Words" on page 110.

The Y chromosome has a distinctive overall structure (figure 6.3) with a short arm and a long arm. At both tips of the Y chromosome are **pseudoautosomal regions**, termed PAR1 and PAR2. They comprise only 5 percent of the chromosome and include 63 pseudoautosomal genes. The term "pseudoautosomal" means that the DNA sequences have counterparts on the X chromosome and can cross over with them. The pseudoautosomal genes encode a variety of proteins that function in both sexes, participating in or controlling bone growth, cell division, immunity, signal transduction, the synthesis of hormones and receptors, fertility, and energy metabolism.

Most of the Y chromosome is the male-specific region, or MSY. (Until the Y chromosome was sequenced in 2003, this portion was called the nonrecombining region.) The MSY lies between the two pseudoautosomal regions, and it consists of three classes of DNA sequences. About 10 to 15 percent of the MSY consists of X-transposed sequences that are 99 percent identical to counterparts on the X chromosome. Protein-encoding genes are scarce here. Another 20 percent of the MSY consists of X-degenerate DNA sequences, which are somewhat similar to X chromosome sequences, and may be remnants of an ancient autosome that long ago gave rise to the X chromosome. The remainder of the MSY includes palindrome-ridden regions, called amplicons. The genes in the MSY include many repeats and specify protein segments that combine in different ways—which is one reason why counting the number of protein-encoding genes on the Y chromosome has been difficult. Many of the genes in the MSY are essential to fertility, including *SRY*.

The Y chromosome was first seen under a light microscope in 1923, and researchers soon recognized its association with



### Figure 6.3 Anatomy of the Y chromosome.

The Y chromosome has two pseudoautosomal regions (PAR1 and PAR2) and a large central area (MSY) that comprises about 95 percent of the chromosome. A few genes are indicated here. *SRY* determines sex. *AZF* encodes a protein essential to producing sperm; mutations in it cause infertility.

maleness. For many years, they sought to identify the gene or genes that determine sex. Important clues came from two very interesting types of people—men who have two X chromosomes (XX male syndrome), and women who have one X and one Y chromosome (XY female syndrome). A close look at their sex chromosomes revealed that the XX males actually had a small piece of a Y chromosome, and the XY females lacked a small part of the Y chromosome. The part of the Y chromosome present in the XX males was the same part that was missing in the XY females. This critical area accounted for half a percent of the Y chromosome. In 1990, researchers isolated and identified the *SRY* gene in this implicated area.

## The Phenotype Forms

The *SRY* gene encodes a very important type of protein called a **transcription factor**, which controls the expression of other genes. The *SRY* transcription factor stimulates



## The Y Wars

Researcher Jennifer Marshall-Graves predicts that the Y chromosome will “self-destruct” within the next 10 million years. Her comparison of Y chromosomes in a wide variety of mammals indicates that, gradually, important genes are being transferred to other chromosomes. David Page, who has led the mapping of the Y chromosome, has a more optimistic view. Each researcher spoke out, in jest, at two scientific conferences. Here is some of what they had to say:

### The Rise and Fall of the Human Y Chromosome

**Jennifer A. Marshall-Graves,**  
Australian National University

The Y chromosome is unique in the human genome. It is small, gene-poor, prone to deletion and loss, variable among species, and useless. You can lack a Y and not be dead, just female. It is impossible to understand why this chromosome is so weird without understanding where it came from. It is a sad decline, and I predict its imminent loss.

The X is a decent sort of chromosome. It accounts for 5 percent of the genome, with about 1,500 perfectly normal genes. The Y is a pathetic little chromosome that has few genes interspersed with lots of junk. And those genes are a weird lot. They are particularly concerned with male sexual development, so they are rather specialized. There are a number of important genes, but some are quite bizarre and many inactive. The Y

shares a lot of sequence with the X, and a lot of homology elsewhere, so the Y clearly diverged from the X.

There are several models of the Y (**figure 1**). The dominant Y model of a macho Y reflects the fact that the Y contains the male-determining *SRY* gene. The selfish Y model predicts that the Y kidnapped genes from elsewhere. The wimp Y model says that the Y is just a relic of the once glorious X chromosome. This model was first proposed by biologist Susumo Ohno in 1967 in the theory that the X and Y originated as a pair of autosomes. Then the Y acquired the male-determining locus, and other genes that are required for spermatogenesis gathered nearby. This led to suppressed recombination in this region of the Y, which allowed all sorts

of horrible genetic accidents to occur that could not be repaired. Mutations, deletions, and insertions accumulated until almost nothing was left, except bits at the top and bottom that still pair with the X. A few genes survived because they found a useful male-specific function, and many of these have made copies of themselves in a desperate race to stave off disappearing altogether.

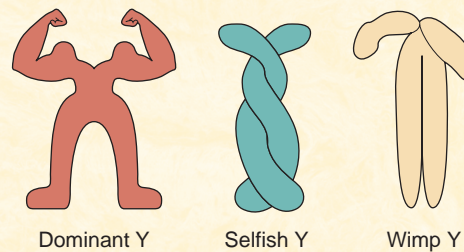
The Y is degrading fast, losing genes at the rate of 5 per million years. I predict that it will be completely gone in 5 to 10 million years. Will we have males? The males in the audience can take comfort from the mole vole *Ellobius lutescens* (**figure 2**). It has no Y, but it does have males and females. It has no *SRY*, no Y chromosome at all. Both sexes are XO. How do they do it? We don't know. Clearly another gene takes over and new sex genes start evolving. Will there be new sex chromosome evolution in humans? Maybe it will happen in different ways in different populations, and we will split into two species.

### Rethinking The Rotting Y Chromosome

**David Page, Massachusetts Institute of Technology and Howard Hughes Medical Institute investigator**

The Y chromosome has had a public relations problem for a long time. For most of the last half of the past century, people thought that the Y chromosome was a junk heap. The genomic junkyard view was the

Models of the Human Y



**Figure 1 Models of the human Y chromosome.** Researcher Jennifer Marshall-Graves offers a tongue-in-cheek look at the Y chromosome, but her research findings are serious—the chromosome is shrinking.

male development by sending signals to the indifferent gonads. In response, sustentacular cells in the developing testis secrete anti-Müllerian hormone, which destroys potential female structures (uterus, uterine tubes, and upper vagina). At the same time, interstitial cells in the testis secrete testosterone, which stimulates the development of male structures (the epididymides, ductus deferentia, seminal vesicles, and ejaculatory ducts). Some testosterone is also converted

to dihydrotestosterone (DHT), which directs the development of the urethra, prostate gland, penis, and scrotum.

Because prenatal sexual development is a multistep process, genetic abnormalities can intervene at several different points (**figure 6.4**). The result may be an XY individual with a block in the gene- and hormone-controlled elaboration of male structures so that a chromosomal he is a phenotypic she. For example, in androgen

insensitivity syndrome (OMIM 300068), caused by a mutation in a gene on the X chromosome, the absence of receptors for androgens (the male sex hormones testosterone and DHT) stops cells in early reproductive structures from receiving the signal to develop as male. The person looks female, but is XY.

Several terms are used to describe individuals whose genetic/chromosomal sex and physical structures, both internal and





**Figure 2 Life without a Y?** Males of all mammals, except two species of mole voles, have Y chromosomes. Birds and reptiles do not. The Y chromosome probably arose from an X chromosome about 310 million years ago. The X lost many genes and gained a few that set their carriers on the road to maleness. This animal is a Y-less male mole vole—it reproduces just fine.

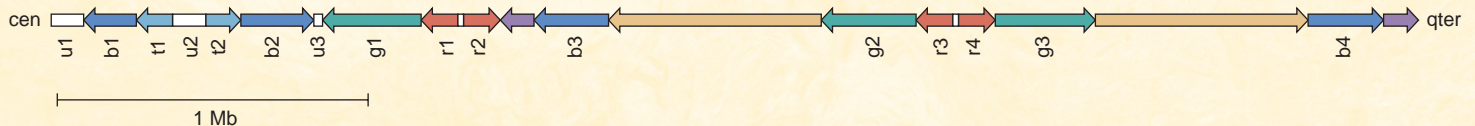
classic model for sex chromosome evolution. We can now update that model.

Back 300 million years ago, when we were reptiles, we had no sex chromosomes, only ordinary autosomes. Shortly after our ancestors parted company with the ancestors of birds, a mutation arose on one member of a pair of ordinary autosomes to give rise to *SRY*. The process of shutting down XY crossing over began, first in the vicinity of *SRY*, and then in an expanding region. Once a piece of the Y was no longer able to recombine with the X, its genes began to rot. The purpose of sex (recombination in meiosis) is not just to generate new gene combinations, but to allow genes to rid themselves of mildly deleterious mutations that accumulate. Y genes are not protected because they have lots of areas of no crossing over. Genes decayed, except for *SRY* and the tips. It wasn't a very flattering model for the Y.

When Jennifer Marshall-Graves and John Aitken wrote their article in *Nature* on the future of sex, that the Y would self-destruct in 10 million years, it truly frightened the people in my lab. We decided we needed to pick up the pace. When the popular press

discovered the story of the impending death of the Y chromosome, they moved the date up to 5 million years from now.

Based on the sequencing of the Y, we've been able to rethink its evolution, and realized that the chromosome may have found a way around its seemingly inevitable problems. We looked closely at the male-specific region of the Y, reanalyzing sequences in a different way, chopped into smaller bits. And we found that each piece would find a match elsewhere on the Y. So segments on the Y are effectively functioning as alleles—30 percent have a perfect match elsewhere on the chromosome. These are not simple repeats, but highly complex sequences of tens to hundreds of kilobases. The region includes eight palindromes and one inverted repeat (**figure 3**). We propose that there is intense recombination within the palindromes. And so the Y has two forms of productive recombination: conventional routine recombination of crossing over with the X at pseudoautosomal regions, and recombination within the Y. It's not that the Y doesn't recombine, it just does it its own way. The Y does copying that preserves its identity.



**Figure 3 The Y chromosome is highly repetitive.** A section of the Y chromosome that David Page studies, called AZFc (for azoospermia factor c), consists of DNA sequences that read the same in either direction, an organization that can lead to instability as well as provide a mechanism to evolve new alleles. Other parts of the chromosome house similar repeats. Matching colors in this depiction represent identical sequences. Same-color arrows that point in opposite directions indicate inverted repeats.

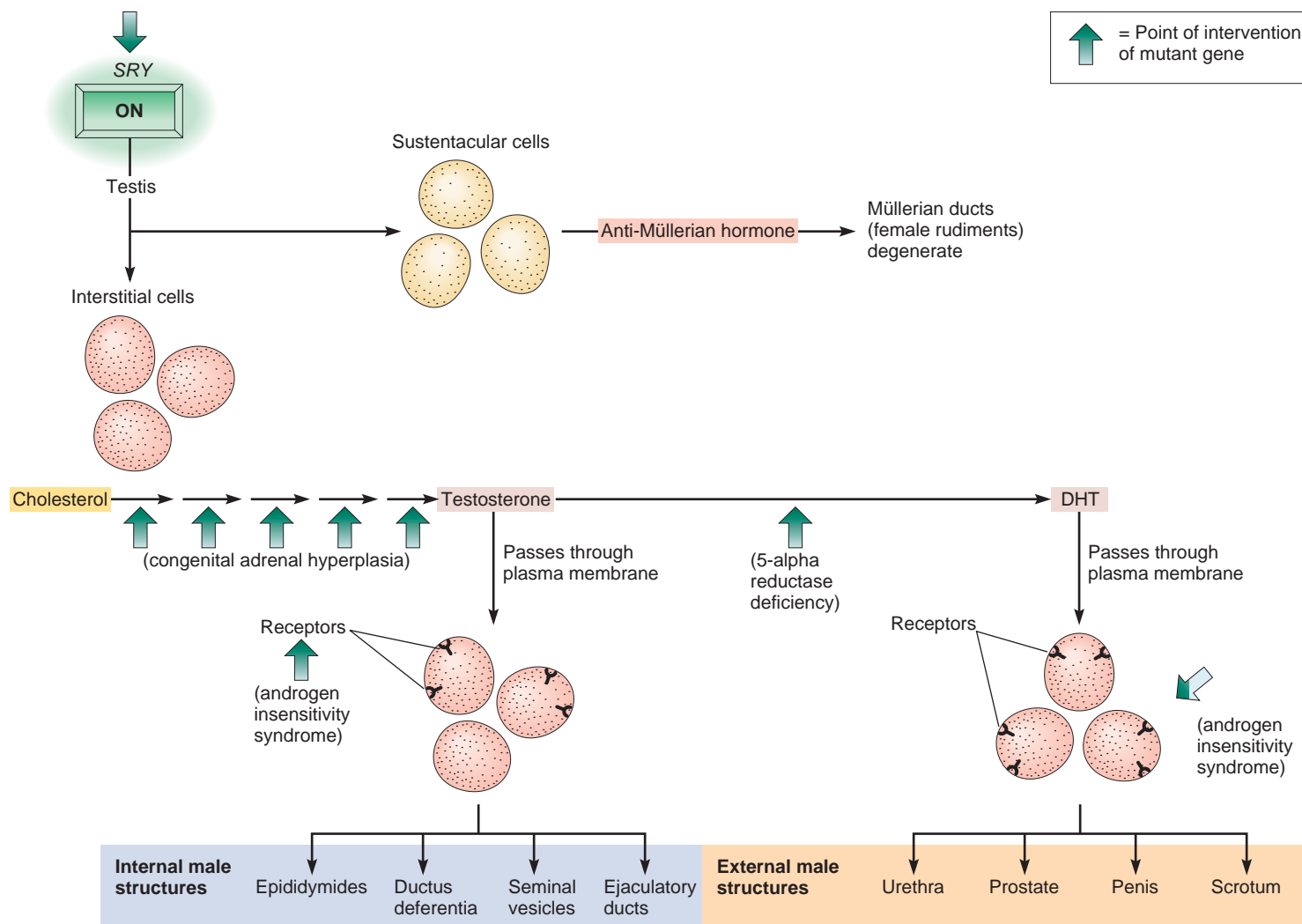
external, are not consistent with one gender. *Hermaphroditism* is an older and more general term for an individual with both male and female sexual structures. The word comes from the Greek god of war, Hermes, and the goddess of love, Aphrodite. *Intersex* refers to individuals whose internal structures are inconsistent with external structures, or whose genitalia are ambiguous. It is the preferred term outside of medical circles. *Pseudohermaphroditism* refers to the

presence of both types of structures but at different stages of life.

Living with pseudohermaphroditism can be quite confusing, and the quality of one's life depends a great deal on how accepting the society is of the condition. Consider 5-alpha reductase deficiency (OMIM 264600), which is autosomal recessive. Affected individuals have a normal Y chromosome, a wild type *SRY* gene, and testes. Testosterone stimulates the Wolffian duct

system to develop into the internal male reproductive tract, while anti-Müllerian hormone eliminates the female precursor structures, so the anatomy makes sense on the inside. The outside is a different story. When 5-alpha reductase, which normally catalyzes the reaction of testosterone to form DHT, is deficient, lack of DHT causes the fetus to develop externally as female—that is, without DHT, a penis cannot form. Changes begin to be noticed at puberty,





**Figure 6.4 Pseudohermaphroditism.** In normal male prenatal development, activation of a set of genes beginning with *SRY* stimulates sustentacular cells to produce hormones that lead to the destruction of female rudiments, and also stimulates interstitial cells to activate the biochemical pathway that produces testosterone and DHT. Testosterone and DHT promote the development of male structures. The green arrows indicate where mutations disrupt normal sexual development. (The ductus deferentia were formerly called vasa deferentia.)

when the adrenal glands, which sit atop the kidneys, start to produce testosterone. This now leads to masculinization. In this XY individual who thought she was a she, the voice deepens, facial hair grows, and muscles begin to build an undeniably masculine physique. Instead of experiencing the expected breast development and menstruation, the clitoris enlarges into a penis. Usually sperm production is normal. XX individuals with 5-alpha reductase deficiency do not have symptoms.

In the Dominican Republic in the 1970s, 22 young girls reached the age of puberty and began to transform into boys. They had a form of 5-alpha reductase deficiency that was fairly common due to consanguinity

(relatives having children with relatives). The parents were happy that they had had sons after all, and so these special adolescents were given their own gender name—guevedoces, for “penis at age 12.” They were fully accepted as whatever they wanted to be. Sadly this isn’t always the case. A compellingly realistic novel, *Middlesex*, tells the story of a young Greek-American man with this condition who grew up as a female.

In a more common form of pseudohermaphroditism, congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (OMIM 201910), an enzyme block leads to testosterone and DHT accumulation. It is autosomal recessive, and both males and females are affected. The

higher levels of androgens cause early puberty in males or male secondary sex characteristics to develop in females. Boys may enter puberty as early as 3 years old, with well-developed musculature, small testes, and an enlarged penis. At birth, girls may have a swollen clitoris that appears to be a small penis. They are female internally, but as they reach puberty, the voice deepens, facial hair grows, and menstruation does not occur.

Prenatal tests that detect chromosomal sex have changed the way that pseudohermaphroditism is diagnosed. Before these tests were available, the condition was detected only after puberty, when masculinization occurred in a person who looked

### Sex Reassignment: Making a Biological “He” into a Social “She”

Identical twins Bruce and Brian Reimer were born in 1965. At age eight months, most of Bruce’s penis was accidentally burned off during a botched circumcision. On the advice of physicians and psychologists, the parents decided to “reassign” Bruce’s gender as female. At 22 months of age, corrective surgery created Brenda from Bruce. The prominent psychologist in charge hailed the transformation a resounding success, and the case came to serve as a precedent for early surgical intervention for children born with “ambiguous genitalia” or structures characteristic of both sexes, a condition termed intersex. About 1 in 2,000 newborns are intersexes, with a few others the result of surgical accidents.

#### Gender Identity Is set

Sex reassignment began to be questioned when the Reimer case came to public attention, because reality for young Brenda was far different from the published descriptions.

Always uneasy in her dress-clad body, Brenda suffered ridicule and confusion, because it was always clear to her and others that she was more than a “tomboy”—she was a boy, despite her surgically altered appearance. Comparison to twin Brian worsened matters. When learning the truth at age 14, “Brenda” threatened suicide unless allowed to live as the correct gender, and so she became David Reimer. He eventually married, adopted stepchildren, and became

a grandfather. He told his story to *Rolling Stone* magazine.

A study published in 2000 supported David’s view that nature contributes more to gender identity than nurture. Researchers at Johns Hopkins University investigated fourteen children with a form of intersex called cloacal exstrophy. They were all XY, and had normal testicles and hormone levels, but no penis. Twelve were reassigned as female but behaved as boys throughout childhood. Six of the twelve declared themselves male between the ages of 5 and 12 years. The two children who were not surgically converted into females live as normal males who lack penises, something that surgery later in life may be able to correct.

#### The Surgical Yardstick

In the past, physicians decided to remove a small or damaged penis and reassign sex as female using a literal yardstick: If a newborn’s stretched organ exceeded an inch, he was deemed a he. If the protrusion was under three-eighths of an inch, she was deemed a she. Organs that fell in between were shortened into a clitoris during the first week of life, and girlhood officially began. Further plastic surgeries and hormone treatments during puberty completed the superficial transformation, with external female tissue sculpted from scrotal tissue. The reverse, creating a penis, is much more difficult and was therefore usually delayed

several months. These surgeries can destroy fertility and sexual sensation.

Easier to surgically treat are babies with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, the most common cause of intersex. The individual is XX but overproduces masculinizing hormones (androgens). The result is a girl with a clitoris so large that it looks like a small penis. Surgical alteration is typically done in adolescence so these young women can take part in decisions affecting their bodies.

Delaying surgery until a person can decide for him or herself may be the best approach for intersex individuals. Sex reassignment surgery is a bioethical issue that involves paternalism, confidentiality, the doctor-patient relationship, and the promise of physicians to “do no harm.” Sums up Alice Dreger of Michigan State University, who has researched intersexuality extensively, “Gender identity is very complicated, and it looks like the various components interact and matter in different ways for different individuals. That’s why unconsenting children and adults should never be subjected to cosmetic, medically unnecessary surgeries designed to alter their sexual tissue. We cannot predict what parts they may want later.”

Perhaps the most compelling evidence that forcing someone to live in the wrong gender can do permanent damage is David Reimer’s fate. He committed suicide in 2004.

female. Today, pseudohermaphroditism is suspected when a prenatal chromosome check reveals an X and a Y chromosome, but the newborn is a phenotypic girl.

Transgender is a poorly understood condition related to sexual identity. A transgendered individual has the phenotype and sex chromosomes of one gender, but feels extremely strongly that he is a she, or vice versa. It is a much more profound condition than transvestitism, which refers to a male who prefers to wear women’s clothing. The

genetic or physical basis of transgender is not known. Some affected individuals undergo surgery so that their physical selves match the gender that they feel certain they are.

#### Is Homosexuality Inherited?

No one really knows why we have feelings of belonging to one gender or the other, but these feelings are intense. Bioethics: Choices for the Future (above) describes

people whose gender identity persists even after surgery alters their phenotype so that it doesn’t match the sex chromosomes.

In homosexuality, a person’s phenotype and genotype are consistent, and physical attraction is toward members of the same sex. Homosexuality is seen in all cultures and has been observed for thousands of years. It has been documented in more than 500 animal species.

Evidence is accumulating that homosexuality is at least partially inherited. Earlier



studies cite the feelings that homosexual individuals have as young children, well before they know of the existence or the meaning of the term. Identical twins are more likely to both be homosexual than are both members of fraternal same-sex twin pairs. Also, two brain areas are of different sizes in homosexual versus heterosexual men.

Research into the inheritance of homosexuality is controversial. In 1993, National Cancer Institute researcher Dean Hamer traced the inheritance of five genetic markers on the X chromosome in 40 pairs of homosexual brothers. Although these DNA sequences are highly variable in the general population, they were identical in 33 of the sibling pairs. Hamer interpreted the finding to mean that genes causing or predisposing a male to homosexuality reside on the X chromosome. However, the work never identified a causative gene. One research group confirmed and extended the work, finding that when two brothers are homosexual and have another brother who is heterosexual, the heterosexual brother does not share the X chromosome markers. This study also did not find the X chromosome markers between pairs of lesbian sisters. Several research groups have refuted Hamer's findings. But a gene controlling homosexuality need not reside on a sex chromosome, where Hamer looked. Ongoing studies are searching among the autosomes for such genes.

In yet another approach to understanding the biological basis of homosexuality, researchers have genetically manipulated male fruit flies to display what looks like homosexual behavior. A mutant allele of an eye color gene called *white* causes the flies to have white eyes when expressed in cells of the eye only. Wild type eye color is red. Researchers altered male fly embryos so that the resulting adult insects expressed the *white* gene in every cell. The altered male flies displayed what appeared to be mating behavior with each other (**figure 6.5**), presumably as a result of the altered gene expression.

The ability to genetically induce homosexual behavior suggests genetic control. The biochemical basis of the phenotype makes sense; the *white* gene's product, an enzyme that controls eye color, enables cells to use the amino acid tryptophan, which is



**Figure 6.5 Is homosexuality inherited?** The ability to genetically alter male fruit flies, causing them to display mating behavior toward each other, adds to evidence that homosexuality is at least partially inherited.

required to manufacture the hormone serotonin. When all the fly's cells express the mutant *white* gene, instead of just eye cells, serotonin levels in the brain drop, and this may cause the unusual behavior. In other animals, lowered brain serotonin is associated with homosexual behavior.

**Table 6.1** summarizes the several components of sexual identity.

**Table 6.1**  
**Sexual Identity**

Level	Events	Timing
Chromosomal/genetic	XY = male XX = female	Fertilization
Gonadal sex	Undifferentiated structure begins to develop as testis or ovary	6 weeks after fertilization
Phenotypic sex	Development of external and internal reproductive structures continues as male or female in response to hormones	8 weeks after fertilization, puberty
Gender identity	Strong feelings of being male or female develop	From childhood, possibly earlier
Sexual orientation	Attraction to same or opposite sex	From childhood

## Sex Ratio

Mendel's law of segregation predicts that populations should have approximately equal numbers of male and female newborns. That is, male meiosis should yield equal numbers of X-bearing and Y-bearing sperm. After birth, societal and environmental factors may favor survival of one gender over the other.

The proportion of males to females in a human population is called the **sex ratio**. Sex ratio is calculated as the number of males divided by the number of females multiplied by 1,000, for people of a particular age. (Some organizations describe sex ratio based on 1.0.) A sex ratio of equal numbers of males and females would be designated 1,000. The sex ratio at conception is called the primary sex ratio. In the United States for the past six decades, newborn boys have slightly outnumbered newborn girls, with the primary sex ratio averaging 1,050. The slight excess of boys may reflect the fact that Y-bearing sperm weigh slightly less than X-bearing sperm, and so they may reach the oocyte faster.

Sex ratio at birth is termed secondary and at maturity is called tertiary. Sex ratio can change markedly with age, reflecting medical conditions that affect the sexes differently, as well as environmental factors that affect one sex more than the other, such as participation in combat or engaging in other dangerous behaviors.



It is interesting to see what happens when a society attempts to alter the sex ratio. This has been done in India and China, where researchers have identified great numbers of “missing females.” In these societies, prenatal diagnostic techniques are used to identify XX fetuses. Termination of XX fetuses, underreporting of female births, and, rarely, selective infanticide of girl babies all have contributed to a very unnaturally skewed sex ratio favoring males.

In China, by the year 2020, 20 million men will find themselves without female partners as a long-term consequence of that nation’s “one child policy.” It began in 1979 to control runaway population growth with financial incentives. If a couple had a second child, the government revoked benefits. Many families wanted their one child to be a male, and so many female pregnancies were unreported or terminated. Although China’s policy prevented hundreds of millions of births, it has today led to a society in which children have few siblings, cousins, aunts, or uncles. Young women are rare. Ironically, Hainan province is now offering housing subsidies for families that have daughters! The tables have turned.

Today the same male bias that happened in China is occurring in India. Based on a survey of 1.1 million families, researchers found that the ratio of boys to girls was about equal when the first or second child was a boy, but if the first child and especially if the first two children were girls, then the secondary sex ratio fell to about 750 girls to every 1,000 boys. Families were using prenatal diagnosis to detect female pregnancies and were terminating about a fourth of them. Researchers estimate that India has about 100 million “missing females.”

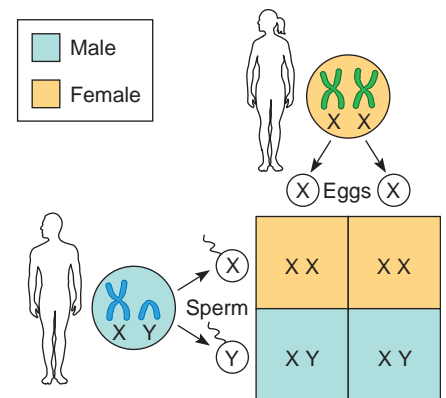
At the other end of the human life cycle, sex ratio favors females in most populations. For people over the age of 65 in the United States, for example, the sex ratio is 720, meaning that there are 72 men for every 100 women. The ratio among older people is the result of disorders that are more likely to be fatal in males as well as behaviors that may shorten their life spans compared to women, such as participating in combat or other violent activities.

## Key Concepts

1. The human female is homogametic (XX) and the male is heterogametic (XY).
2. The Y chromosome has few genes. It includes two small pseudoautosomal regions and a large male-specific region that does not recombine. Most of this region is palindromic sequences that may maintain the chromosome’s structure. Other Y sequences are similar to sequences on the X chromosome.
3. Activation of the *SRY* gene on the Y chromosome starts a cascade of gene action that causes the undifferentiated gonad to develop into a testis. Then, sustentacular cells in the testis secrete anti-Müllerian hormone, which stops the development of female structures. Interstitial cells in the testis secrete testosterone, which stimulates the development of male internal structures. Testosterone is also converted to DHT, which directs the development of external structures. In several disorders, chromosomal, gonadal, and/or phenotypic sex are inconsistent.
4. Genes probably contribute to homosexuality.
5. Sex ratio is the number of males divided by the number of females multiplied by 1,000, for people of a particular age.

## 6.2 Traits Inherited on Sex Chromosomes

Genes carried on the Y chromosome are said to be **Y-linked**, and those on the X chromosome are **X-linked**. Y-linked traits are rare because the chromosome has few genes, and many have counterparts on the X chromosome. These traits are passed from male to male, because a female does not have a Y chromosome. No other Y-linked traits besides infertility (which obviously can’t be passed on) are yet clearly defined, although certain gene products have been identified. Claims that “hairy ears” is a Y-linked trait did not hold up—it turned out that families hid their affected female members!



**Figure 6.6 Sex determination in humans.** An oocyte has a single X chromosome. A sperm cell has either an X or a Y chromosome. If a Y-bearing sperm cell with a functional *SRY* gene fertilizes an oocyte, the zygote is a male (XY). If an X-bearing sperm cell fertilizes an oocyte, then the zygote is a female (XX).

Genes on the X chromosome have different patterns of expression in females and males, because a female has two X chromosomes and a male just one. In females, X-linked traits are passed just like autosomal traits—that is, two copies are required for expression of a recessive allele, and one copy for a dominant allele. In males, however, a single copy of an X-linked allele causes expression of the trait or illness because there is no copy of the gene on a second X chromosome to mask the other’s effect. A man inherits an X-linked trait only from his mother. The human male is considered **hemizygous** for X-linked traits, because he has only one set of X-linked genes.

Understanding how sex chromosomes are inherited is important in predicting phenotypes and genotypes in offspring. A male inherits his Y chromosome from his father and his X chromosome from his mother (**figure 6.6**). A female inherits one X chromosome from each parent. If a mother is heterozygous for a particular X-linked gene, her son or daughter has a 50 percent chance of inheriting either allele from her. X-linked traits are always passed on the X chromosome from mother to son or from either parent to daughter, but there can be no direct male-to-male transmission of X-linked traits.

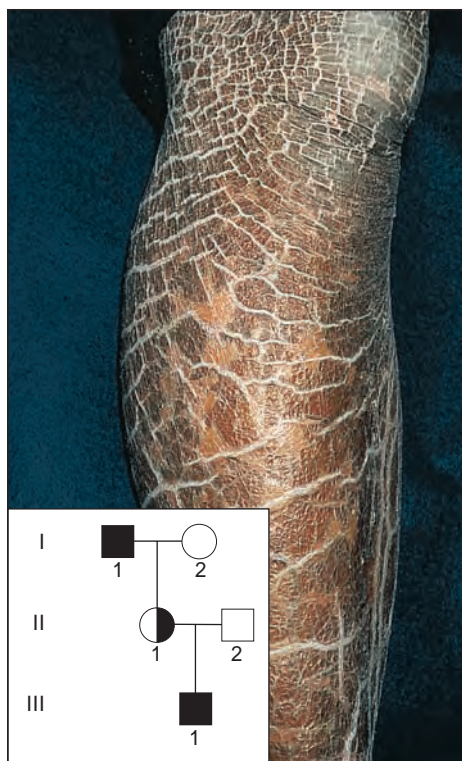
## X-Linked Recessive Inheritance

An X-linked recessive trait is expressed in females if the causative allele is present in two copies. Many times, an X-linked trait passes from an unaffected heterozygous mother to an affected son. **Table 6.2** summarizes the transmission of an X-linked recessive trait.

If an X-linked condition is not lethal, a man may be healthy enough to transmit it to offspring. Consider the small family depicted in **figure 6.7**. A middle-aged man who had rough, brown, scaly skin did not realize his condition was inherited until his daughter had a son. By a year of age, the boy's skin resembled his grandfather's. In the condition, called ichthyosis (OMIM 308100), an enzyme deficiency blocks removal of cholesterol from skin cells. The upper skin layer cannot peel off as it normally does, causing a brown, scaly appearance. A test of the daughter's skin cells revealed that she produced half the normal amount of the enzyme, indicating that she was a carrier.

Colorblindness is another X-linked recessive trait that does not hamper the ability of a man to have children. About 8 percent of males of European ancestry are colorblind, as are 4 percent of males of African descent. Only 0.4 percent of females in both groups are colorblind. Reading 6.1, on page 120, takes a closer look at this interesting trait.

**Figure 6.8** shows part of an extensive pedigree for another X-linked recessive trait, the blood-clotting disorder hemophilia A (OMIM 306700). Note the combination of pedigree symbols and a



**Figure 6.7 An X-linked recessive trait.** Ichthyosis is transmitted as an X-linked recessive trait. A grandfather and grandson were affected in this family.

Punnett square to trace transmission of the trait. Dominant and recessive alleles are indicated by superscripts to the X and Y chromosomes. In the royal families of England, Germany, Spain, and Russia, the mutant allele arose in one of Queen Victoria's X chromosomes; it was either a new mutation or she inherited it. In either case, she passed it on through carrier daughters and one mildly affected son.

The transmission pattern of hemophilia A is consistent with the criteria for an X-linked recessive trait listed in table 6.2. A daughter can inherit an X-linked recessive disorder or trait if her father is affected and her mother is a carrier, because the daughter inherits one affected X chromosome from each parent. Without a biochemical test, though, an unaffected woman would not know she is a carrier for an X-linked recessive trait unless she has an affected son. A genetic counselor can estimate a potential carrier's risk using probabilities derived from Mendel's laws, combined with knowledge of X-linked inheritance patterns.

Consider a woman whose brother has hemophilia A. Both her parents are healthy, but her mother must be a carrier because her brother is affected. The woman's chance of being a carrier is  $1/2$  (or 50 percent), which is the chance that she has inherited the X chromosome bearing the hemophilia allele from her mother. The chance of the woman conceiving a son is  $1/2$ , and of that son inheriting hemophilia is  $1/2$ . Using the product rule, the risk that she is a carrier and will have a son with hemophilia, out of all the possible children she can conceive, is  $1/2 \times 1/2 \times 1/2$ , or  $1/8$ .

**Table 6.3** lists several X-linked disorders. Most genes on the X chromosome are not actually related to sex determination, and are necessary for normal development or physiology in both sexes.

## X-Linked Dominant Inheritance

Dominant X-linked conditions and traits are rare. Again, gene expression differs between the sexes (**table 6.4**). A female who inherits a dominant X-linked allele has the associated trait or illness, but a male who inherits the allele is usually more severely affected because he has no other allele to mask its effect. The children of a normal man and a woman with a dominant, disease-causing allele on the X chromosome face the risks summarized in **figure 6.9**.

An example of an X-linked dominant condition is incontinentia pigmenti (IP) (OMIM 308300). In affected females, swirls of skin pigment arise when melanin penetrates the deeper skin layers. A newborn girl with IP has yellow, pus-filled vesicles on her limbs that come and go over the first few weeks. Then the lesions become warty and eventually give way to brown splotches that may remain for life, although they fade with time. Males with the condition are so severely affected that they do not survive to be born. This is why women with the disorder have a miscarriage rate of about 25 percent.

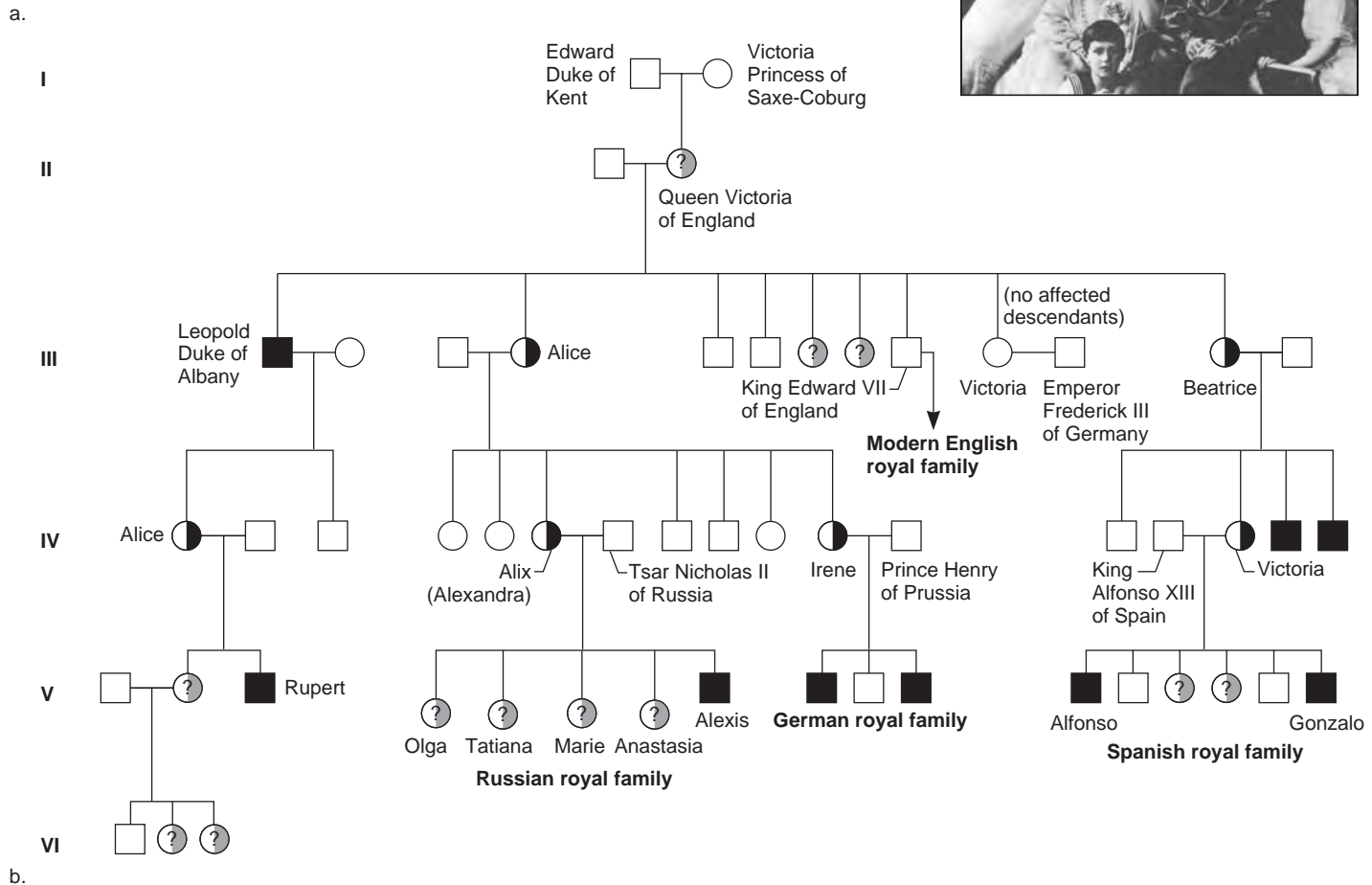
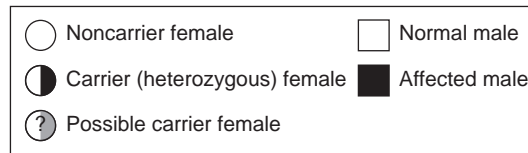
The gene that causes IP (called *NEMO*) activates genes that carry out the immune response and apoptosis in tissues that derive from ectoderm, such as skin, hair, nails, eyes, and the brain. Genetic tests can detect the deletion (missing DNA) that causes most cases.

**Table 6.2**

### Criteria for an X-Linked Recessive Trait

1. Always expressed in the male.
2. Expressed in a female homozygote but very rarely in a heterozygote.
3. Passed from heterozygote or homozygote mother to affected son.
4. Affected female has an affected father and a mother who is affected or a heterozygote.

	$X^H$	$X^h$
$X^H$	$X^H X^H$ Normal daughter	$X^H X^h$ Carrier daughter
$Y$	$X^H Y$ Normal son	$X^h Y$ Son with hemophilia



**Figure 6.8 Hemophilia** (a) This X-linked recessive disease usually passes from a heterozygous woman (designated  $X^H X^h$ , where  $h$  is the hemophilia-causing allele) to heterozygous daughters or hemizygous sons. The father is normal. (b) The disorder has appeared in the royal families of England, Germany, Spain, and Russia. The mutant allele apparently arose in Queen Victoria, who passed it to Alice and Beatrice, who were carriers, and to Leopold, who had a mild enough case that he fathered children. In the fourth generation, Alexandra was a carrier who married Nicholas II, Tsar of Russia. Alexandra's sister Irene married Prince Henry of Prussia, passing the allele to the German royal family, and Beatrice's descendants passed it to the Spanish royal family. This figure depicts only part of the extensive pedigree. The modern royal family in England does not carry hemophilia.

Another X-linked dominant condition, congenital generalized hypertrichosis (OMIM 307150), produces many extra hair follicles, and hence denser and more abundant upper body hair (**figure 6.10**). Hair growth is milder and patchier in females because of hormonal differences and the presence of a second X chromosome.

Figure 6.10b shows part of a pedigree of a large Mexican family with 19 affected members. Note the pattern of X-linked dominant inheritance. The affected man in the pedigree passed the trait to all four daughters, but to none of his nine sons. Because sons inherit the X chromosome from their mother, and only the Y from their father,

they could not have inherited the hairiness from their father.

### Solving a Problem: X-Linked Inheritance

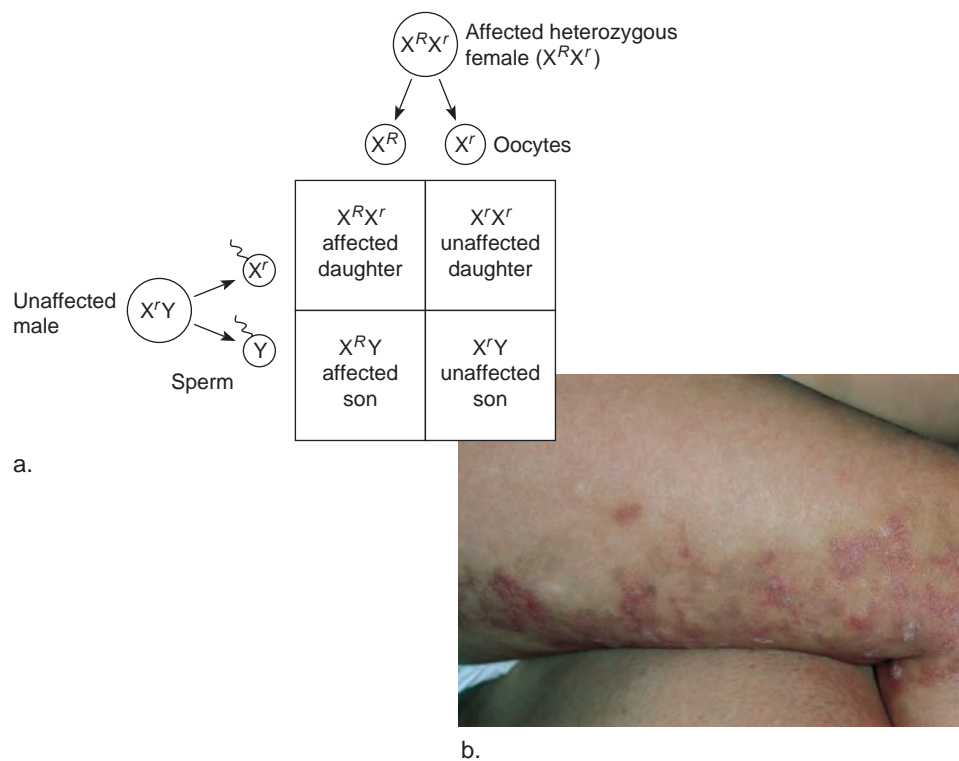
Mendel's first law (segregation) applies to genes on the X chromosome. Therefore, the same



Table 6.3

## Some Disease-Related Genes on the Human X Chromosome

Condition (r = recessive; D = dominant)	OMIM #	Symptoms
Agammaglobulinemia (r)	300300	Lack of certain antibodies
Alport syndrome (r)	301050	Deafness, kidney inflammation
Amelogenesis imperfecta (D)	301200	Abnormal tooth enamel
Anhidrotic ectodermal dysplasia (r)	305100	No teeth, hair, sweat glands
Chronic granulomatous disease (r)	306400	Skin and lung infections, enlarged liver and spleen
Diabetes insipidus (r)	304800	Copious urination
Duchenne muscular dystrophy (r)	310200	Progressive muscle weakness
Fabry disease (r)	301500	Abdominal pain, skin lesions, kidney failure
Hypophosphatemia (D and r)	307800	Vitamin-D-resistant rickets
Lesch-Nyhan syndrome (r)	300322	Mental retardation, self-mutilation, urinary stones, spastic cerebral palsy
Megalocornea (r)	249300	Enlarged cornea
Menkes disease (r)	309400	Kinky hair, brain degeneration, abnormal copper transport
Norrie disease (r)	310600	Eye degeneration
Ornithine transcarbamylase deficiency (rr)	311250	Mental deterioration, ammonia in blood
Retinitis pigmentosa (r and D)	312612	Constriction of visual field, nightblindness, clumps of pigment in eye
Rett syndrome (D)	312750	Mental retardation, neurodegeneration
Severe combined immune deficiency (r)	300400	Lack of T and B lymphocytes
Wiskott-Aldrich syndrome (r)	301000	Bloody diarrhea, infections, rash, bleeding



**Figure 6.9 X-linked dominant inheritance.** (a) A female who has an X-linked dominant trait has a 1 in 2 probability of passing it to her offspring, male or female. Males are generally more severely affected than females. (b) Note the characteristic patchy pigmentation on the leg of a girl who has incontinentia pigmenti.

Table 6.4

## Criteria for an X-Linked Dominant Trait

1. Expressed in female in one copy.
2. Much more severe effects in males.
3. High rates of miscarriage due to early lethality in males.
4. Passed from male to all daughters but to no sons.

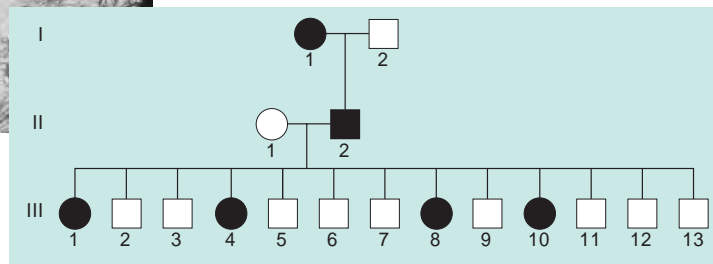
logic is used to solve problems as to trace traits transmitted on autosomes, with the added step of considering the X and Y chromosomes in Punnett squares. Follow these steps:

1. Look at the pattern of inheritance. Different frequencies of affected males and females in each generation may suggest X linkage. For an X-linked recessive trait:
  - An affected male has a carrier mother.
  - An unaffected female with an affected brother has a 50 percent (1 in 2) chance of being a carrier.
  - An affected female has a carrier or affected mother *and* an affected father.



a.

**Figure 6.10 An X-linked dominant condition.** (a) This six-year-old child has congenital generalized hypertrichosis. (b) In this partial pedigree of a large Mexican family, the affected male in the second generation passed the condition to all of his daughters and none of his sons. This is because he transmits his X chromosome only to females.



b.

- A carrier (female) has a carrier mother *or* an affected father.
- For an X-linked dominant trait:
- There may be no affected males, because they die early.
- An affected female has an affected mother.

2. Draw the pedigree.
3. List all genotypes and phenotypes and their probabilities.
4. Assign genotypes and phenotypes to the parents. Consider clues in the phenotypes of relatives.
5. Determine how alleles separate into gametes for the genes of interest on the X and Y chromosomes.
6. Unite the gametes in a Punnett square.
7. Determine the phenotypic and genotypic ratios for the  $F_1$  generation.
8. To predict further generations, use the genotypes of the  $F_1$  and repeat steps 4 through 6.

Consider Kallmann syndrome (OMIM 308700), which causes very poor or absent sense of smell and small testes or ovaries. It is X-linked recessive. Tanisha does not have Kallmann syndrome, but her brother Jamal and her maternal cousin Malcolm (her mother's sister's child) have it. Tanisha's and Malcolm's parents are unaffected, as is Tanisha's husband Sam. Tanisha and Sam wish to know the risk that a son would

inherit the condition. Sam has no affected relatives.

### Solution

1. Mode of inheritance: The trait is X-linked recessive because males are affected through carrier mothers.

Genotypes	Phenotypes
$X^KX^K$ , $X^KX^k$ , $X^KY$	normal
$X^kX^k$ , $X^kY$	affected

Individual	Genotype	Phenotype	Probability
Tanisha	$X^KX^K$ or $X^KX^k$	normal (carrier)	50% each
Jamal	$X^kY$	affected	100%
Malcolm	$X^kY$	affected	100%
Sam	$X^KY$	normal	100%

4. Tanisha's gametes

if she is a carrier:  $X^K$   $X^k$   
 Sam's gametes:  $X^K$  Y

5. Punnett Square

	$X^K$	$X^k$
$X^K$	$X^KX^K$	$X^KX^k$
Y	$X^KY$	$X^kY$

6. Interpretation: If Tanisha is a carrier, the probability that their son will have Kallmann syndrome is 50 percent, or 1 in 2. (Note that this is a conditional probability. The chance that any particular son will have the condition is actually 1 in 4, because Tanisha also has a 50 percent chance of being genotype  $X^KX^K$  and therefore not a carrier.)

## Key Concepts

1. Y-linked traits are passed on the Y chromosome, and X-linked traits on the X.
2. Because a male is hemizygous, he expresses all the genes on his X chromosome, whereas a female expresses recessive alleles on the X chromosome only if she is homozygous recessive.
3. X-linked recessive traits have a 50 percent probability of passing from carrier mothers to sons.
4. X-linked dominant conditions are expressed in both males and females but are more severe in males.
5. Mendel's first law can be used to solve problems involving X-linked genes.

## 6.3 Sex-Limited and Sex-Influenced Traits

An X-linked recessive trait generally is more prevalent in males than females. Other situations, however, can affect gene expression in the sexes differently.

### Sex-Limited Traits

A **sex-limited trait** affects a structure or function of the body that is present in only males or only females. Such a gene may be X-linked or autosomal.

Understanding sex-limited inheritance is important in animal breeding. For example, a New Zealand cow named Marge, who has a mutation that makes her milk very low in saturated fat, is founding a commercial herd. Males play their part by transmitting the mutation, even though they do not make milk. In humans, beard growth is sex-limited. A woman does not grow a beard because she does not manufacture the hormones required for facial hair growth. She can, however, pass to her sons the genes specifying heavy beard growth.

An inherited medical condition that arises during pregnancy is obviously sex-limited, but the male genome contributes to the development of supportive structures, such as the placenta. This is the case for preeclampsia, a sudden

when two forms of that protein are made in the female heterozygote, the signal is disrupted in a way that blocks the cells that form the sutures of the skull from joining cleanly.

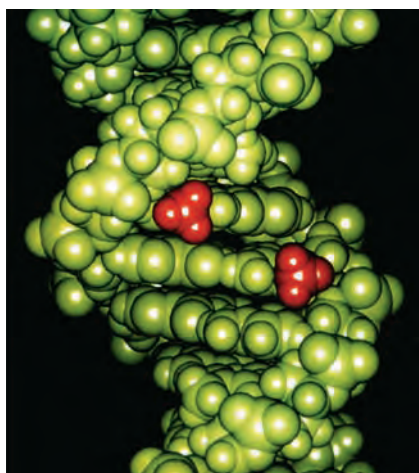
## Key Concepts

1. In female mammals, X inactivation compensates for differences between males and females in the numbers of gene copies on the X chromosome.
2. Early in development, one X chromosome in each cell of the female is turned off.
3. The effects of X inactivation can be noticeable when heterozygous alleles are expressed in certain tissues.

## 6.5 Genomic Imprinting

In Mendel's pea experiments, it didn't matter whether a trait came from the male or female parent. For certain genes in mammals, however, parental origin does influence the phenotype. These genes are said to be imprinted. In **genomic imprinting**, a molecule covers a gene or several linked genes and prevents them from being accessed to synthesize protein (**figure 6.15**). The molecule, a methyl group, is a carbon atom bonded to three hydrogen atoms ( $\text{CH}_3$ ).

For a particular imprinted gene, the copy inherited from either the father or the mother is always covered with methyls, even in different individuals. The result of this gene cloaking is that a disease may be



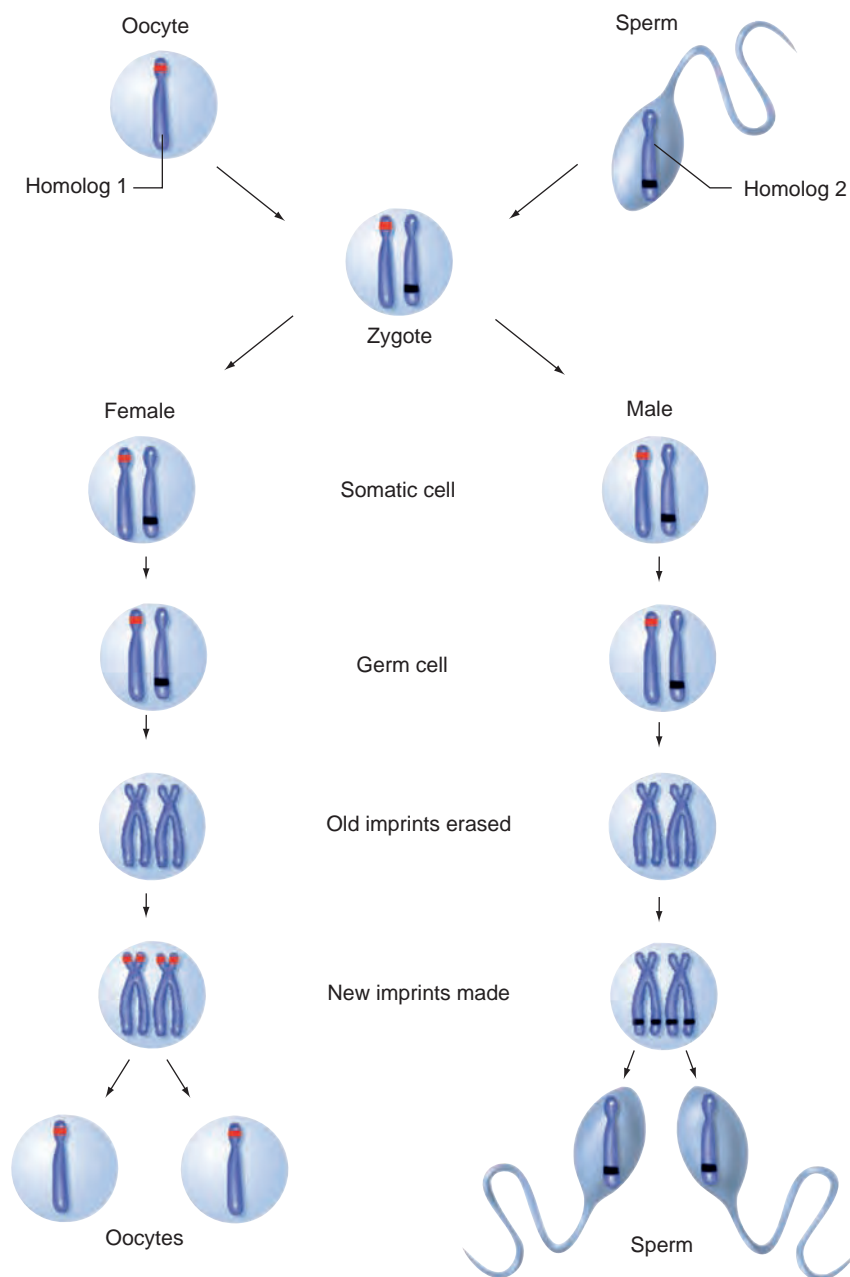
**Figure 6.15** Methyl ( $\text{CH}_3$ ) groups "silence" certain genes.

more severe, or different, depending upon which parent transmitted the gene. That is, a particular gene might function if it came from the father, but not if it came from the mother, or vice versa.

## Silencing the Contribution From One Parent

Imprinting is an epigenetic alteration. It is a layer of meaning stamped upon a gene without changing its DNA sequence. The imprinting pattern is passed from cell to cell

in mitosis, but not from individual to individual through meiosis. When silenced DNA is replicated during mitosis, the pattern of blocked genes is exactly placed, or imprinted, on the new DNA, covering the same genes as in the parental DNA (**figure 6.16**). In this way, the "imprint" of inactivation is perpetuated, as if each such gene "remembers" which parent it came from. In meiosis, however, imprints are removed and reset. As oocyte and sperm form, the  $\text{CH}_3$  groups shielding their imprinted genes are stripped away, and new patterns are set



**Figure 6.16 Genomic imprinting.** Imprints are erased during meiosis, then reinstituted according to the sex of the new individual.



## Reading 6.1

# Of Preserved Eyeballs and Duplicated Genes—Colorblindness

English chemist John Dalton saw things differently from most people. In a 1794 lecture, he described his visual world. Sealing wax that appeared red to other people was as green as a leaf to Dalton and his brother. Pink wildflowers were blue, and Dalton perceived the cranesbill plant as “sky blue” in daylight, but “very near yellow, but with a tincture of red,” in candlelight. He concluded, “that part of the image which others call red, appears to me little more than a shade, or defect of light.” The Dalton brothers had X-linked recessive colorblindness.

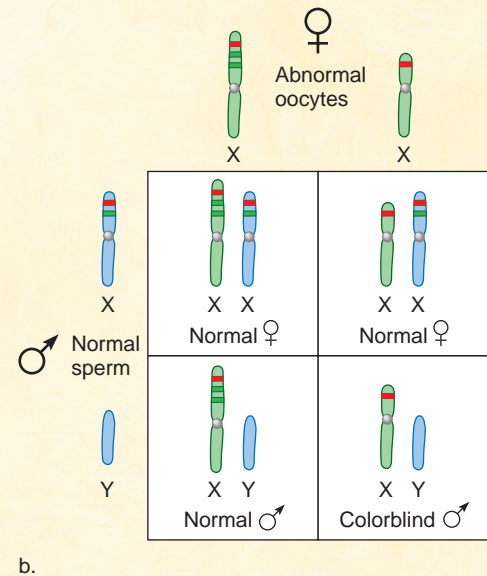
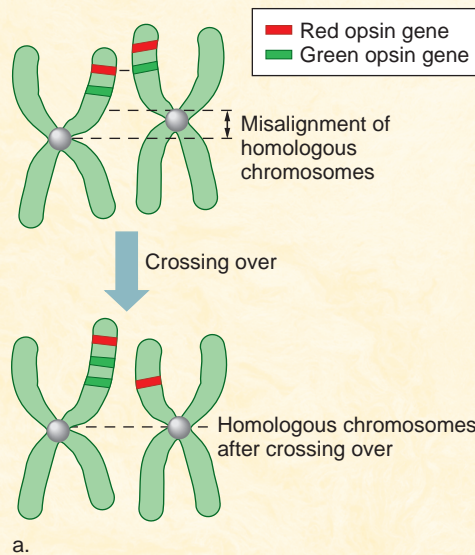
Curious about the cause of his colorblindness, Dalton asked his personal physician, Joseph Ransome, to dissect his eyes after he died. Ransome snipped off the back of one eye, removing the retina, where the cone cells that provide color vision are nestled among the more abundant rod cells that impart black-and-white vision. Because Ransome could see red and green normally when he peered through the back of his friend’s eyeball, he concluded that it was not an abnormal filter in front of the eye that altered color vision. He stored the eyes in dry air, enabling researchers at the London Institute of Ophthalmology to analyze DNA in Dalton’s eyeballs in 1994. Dalton’s remaining retina lacked one of the three types of photopigments that enable cone cells to capture certain wavelengths of light.

### Color Vision Basics

Cone cells are of three types, defined by the presence of any of three types of photopigments. An object appears colored because it reflects certain wavelengths of light, and each cone type captures a particular range of wavelengths with its photopigment. The

brain then interprets the incoming information as a visual perception, much as an artist mixes the three primary colors to create many hues and shadings.

Each photopigment has a vitamin A-derived portion called retinal and a protein portion called an opsin. The presence of



**Figure 1 How colorblindness arises.** (a) The sequence similarities among the opsin genes responsible for color vision may cause chromosomes to misalign during meiosis in the female. Offspring may inherit too many, or too few, opsin genes. A son inheriting an X chromosome missing an opsin gene would be colorblind. A daughter, unless her father is colorblind, would be a carrier. (b) A missing gene causes X-linked colorblindness.

rise in blood pressure late in pregnancy. It kills 50,000 women worldwide each year. A study of 1.7 million pregnancies in Norway found that if a man’s first wife had preeclampsia, his second wife had double the risk of developing the condition, too. Another study found that women whose mothers-in-law developed preeclampsia when pregnant with the women’s husbands had approximately twice the rate of developing the condition themselves. Perhaps a gene from the father affects the placenta in a way that elevates the pregnant woman’s blood pressure.

### Sex-Influenced Traits

In a **sex-influenced trait**, an allele is dominant in one sex but recessive in the other. Such a gene may be X-linked or autosomal. The difference in expression can be caused by hormonal differences between the sexes. For example, an autosomal gene for hair growth pattern has two alleles, one that produces hair all over the head and another that causes pattern baldness (**figure 6.11**). The baldness allele is dominant in males but recessive in females, which is why more men than women are bald. A heterozygous male

is bald, but a heterozygous female is not. A bald woman is homozygous recessive. Even a bald woman tends to have some wisps of hair, whereas an affected male may be completely hairless on the top of his head.

### Key Concepts

1. A sex-limited trait affects body parts or functions present in only one gender.
2. A sex-influenced allele is dominant in one sex but recessive in the other.



retinal in photopigments explains why eating carrots, rich in vitamin A, promotes good vision. The presence of opsins—because they are controlled by genes—explains why colorblindness is inherited. The three types of opsins correspond to short, middle, and long wavelengths of light. Mutations in opsin genes cause three different types of colorblindness.

A gene on chromosome 7 encodes short-wave opsins, and mutations in it produce the rare autosomal “blue” form of colorblindness (OMIM 190900). Dalton had deuteranopia (green colorblindness), which means his eyes lacked the middle-wavelength opsin. In the third type, protanopia (red colorblindness), long-wavelength opsin is absent. Deuteranopia (OMIM 303800) and protanopia (OMIM 303900) are X-linked.

### Molecular Analysis

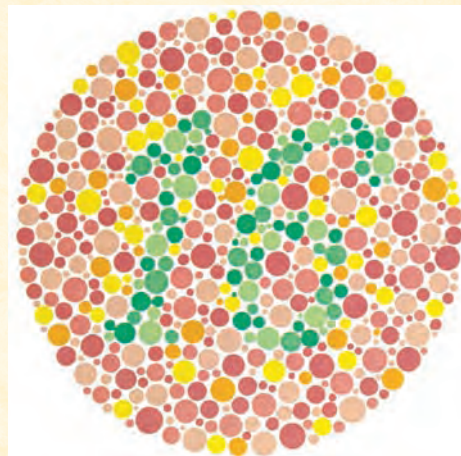
Jeremy Nathans of Johns Hopkins University is another researcher who has personally contributed to our understanding of color vision. First, he used a cow version of a protein called rhodopsin that provides black-and-white vision to identify the human counterpart of the rhodopsin gene. Hypothesizing that the DNA sequence in the rhodopsin gene would be similar to that in the three opsin genes, and therefore able to bind to them, Nathans used the human rhodopsin gene as a “probe”

to search his own DNA for genes with similar sequences. He found three. One was on chromosome 7, the other two on the X chromosome.

Although Nathans can see colors, his opsin genes are not entirely normal, which provided a big clue to how colorblindness arises and why it is so common. On his X chromosome, Nathans has one red opsin gene and two green genes, instead of the normal one of each. Because the red and green genes have similar sequences, Nathans reasoned, they can misalign during meiosis in the female (**figure 1**). The resulting oocytes would then have either two or none of one opsin gene type. An oocyte lacking

either a red or a green opsin gene would, when fertilized by a Y-bearing sperm, give rise to a colorblind male.

People who are colorblind must get along in a multicolored world. To help them overcome the disadvantage of not seeing important color differences, computer algorithms can convert colored video pictures into shades they can see. **Figure 2** shows one of the tests typically used to determine whether someone is colorblind. Absence of one opsin type prevents affected individuals from seeing a different color in certain circles in the figure. These individuals cannot perceive a particular embedded pattern that other people can see.



**Figure 2 A test for colorblindness.** Males with red-green colorblindness cannot see the number 16 within this pattern of circles, as a person with normal color vision can. Reproduced from *Ishihara's Tests for Color Deficiency* published by Kanehara Trading Inc., located at Tokyo in Japan. But tests for color deficiency cannot be conducted with this material. For accurate testing, the original plates should be used.

## 6.4 X Inactivation

Females have two alleles for every gene on the X chromosome, whereas males have only one. In mammals, a mechanism called **X inactivation** balances this apparent inequality in the expression of genes on the X chromosome.

### Equaling Out the Sexes

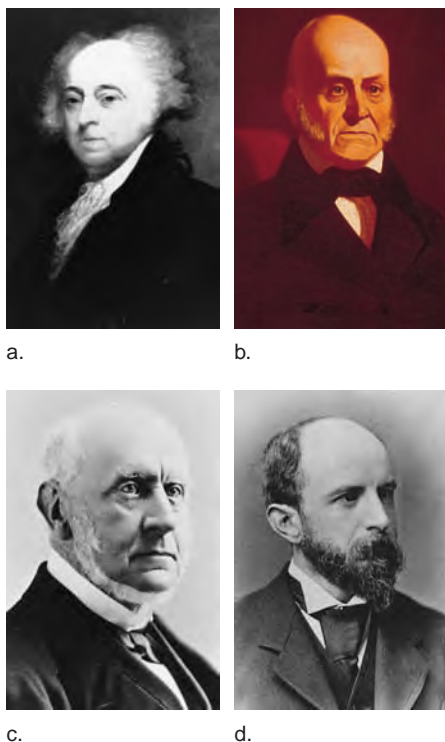
Early in the development of the female embryo, about 75 percent of the genes on one X chromosome in each cell are inactivated, and the remaining 25 percent are

expressed to different degrees in different women. Which X chromosome is mostly turned off in each cell—the one inherited from the mother or the one from the father—is random. As a result, a female mammal expresses the X chromosome genes inherited from her father in some cells and those from her mother in others. She is, therefore, a mosaic for expression of most genes on the X chromosome (**figure 6.12**).

By studying rare human females who have lost a small part of one X chromosome, researchers identified a specific region, the X inactivation center, that shuts off much of the chromosome. Genes in the PARs and

some other genes escape inactivation. A gene called *XIST* controls X inactivation. It encodes an RNA that binds to a specific site on the same (inactivated) X chromosome. From this point out to the chromosome tip, the X chromosome is inactivated.

Once an X chromosome is inactivated in one cell, all its daughter cells have the same X chromosome inactivated. Because the inactivation occurs early in development, the adult female has patches of tissue that differ in their expression of X-linked genes. With each cell in her body having only one active X chromosome, she is chromosomally equivalent to the male.

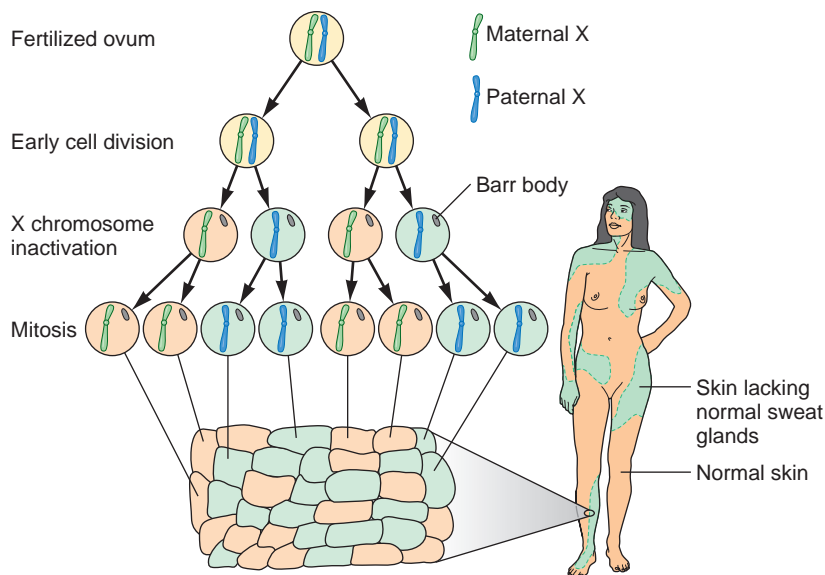


**Figure 6.11** Pattern baldness is a sex-influenced trait that affected the Adams family. John Adams (1735–1826) **(a)** was the second president of the United States and the father of John Quincy Adams (1767–1848) **(b)**, the sixth president. John Quincy was the father of Charles Francis Adams (1807–1886) **(c)**, a diplomat and the father of historian Henry Adams (1838–1918) **(d)**.

X inactivation can alter the phenotype (gene expression), but not the genotype. It is not permanent, and is reversed in germline cells destined to become oocytes. Therefore, a fertilized ovum does not have an inactivated X chromosome.

X inactivation is an example of an epigenetic change—one that is passed from one cell generation to the next but that does not alter the DNA base sequence. We can observe X inactivation at the cellular level because the turned-off X chromosome absorbs a stain much faster than the active X. This differential staining occurs because inactivated DNA has chemical methyl ( $\text{CH}_3$ ) groups that prevent it from being transcribed into RNA and also enable it to absorb stain.

X inactivation can be used to check the sex of an individual. The nucleus of a cell of a female, during interphase, has one dark-staining X chromosome called a **Barr body**. A cell from a male has no Barr body because his one X chromosome remains active.



**Figure 6.12 X inactivation.** A female is a mosaic for expression of genes on the X chromosome because of the random inactivation of either the maternal or paternal X in each cell early in prenatal development. In anhidrotic ectodermal dysplasia, a woman has patches of skin that lack sweat glands and hair. (Colors distinguish cells with the inactivated X, not to depict skin color.)

In 1961, English geneticist Mary Lyon proposed that the Barr body is the inactivated X chromosome and that it is turned off in early development. Checking for Barr bodies has been done in the Olympics to identify athletes competing as the wrong gender.

## Effect on the Phenotype

The consequence of X inactivation on the phenotype can be interesting. For homozygous X-linked genotypes, X inactivation has no effect. No matter which X chromosome is turned off, the same allele is left to be expressed. For heterozygotes, however, X inactivation leads to expression of one allele or the other. This doesn't affect health if enough cells express the functional gene product. However, some traits reveal the X inactivation. The swirls of skin color in incontinentia pigmenti (IP) patients reflect patterns of X inactivation in skin cells. Where the normal allele for melanin pigment is shut off, pale swirls develop. Where pigment is produced, brown swirls result.

A female who is heterozygous for an X-linked recessive gene can express the associated condition if the normal allele is inactivated in the tissues that the illness affects. Consider a carrier of hemophilia A. If the X chromosome carrying the normal allele for the clotting factor is turned off in the liver, then the woman's blood will clot slowly

enough to cause mild hemophilia. (Luckily for her, slowed clotting time also greatly reduces her risk of cardiovascular disease caused by blood clots blocking circulation.) A carrier of an X-linked trait who expresses the phenotype is called a **manifesting heterozygote**.

Whether or not a manifesting heterozygote results from X inactivation depends upon how adept cells are at sharing. Consider two lysosomal storage disorders, which are deficiencies of specific enzymes that normally dismantle cellular debris in lysosomes. In Hunter syndrome (OMIM 309900, also called mucopolysaccharidosis II), cells that make the enzyme readily send it to neighboring cells that do not, essentially correcting the defect in cells that can't make the enzyme. Carriers of Hunter syndrome do not have symptoms because cells get enough enzyme. Affected boys are deaf, mentally retarded, have dwarfism and abnormal facial features, heart damage, and enlarged liver and spleen.

In Fabry disease (OMIM 301500, also called alpha-galactosidase A deficiency) the enzyme is not easily released from cells, so a female who is a heterozygote may have cells in the affected organs that lack the enzyme. She may develop mild symptoms of this disorder that causes skin lesions, abdominal pain, and kidney failure in boys.

A more familiar example of X inactivation is the coat colors of tortoiseshell

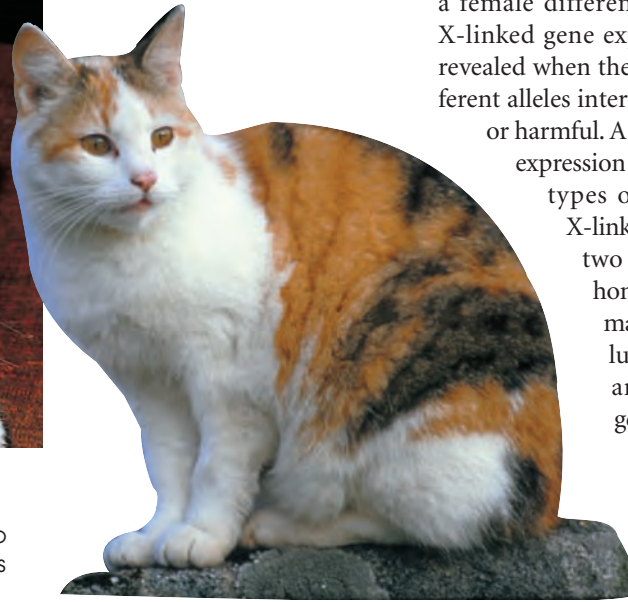




a.

### Figure 6.13 Visualizing X inactivation.

X inactivation is obvious in tortoiseshell (a) and calico (b) cats. X inactivation is rarely observable in humans because most cells do not remain together during development, as a cat's skin cells do.



b.

and calico cats. An X-linked gene confers brownish-black (dominant) or yellowish-orange (recessive) color. A female cat heterozygous for this gene has patches of each color, forming a tortoiseshell pattern that reflects different cells expressing either of the two alleles (figure 6.13). The earlier the X inactivation, the larger the patches, because more cell divisions can occur after the event, producing more daughter cells. White patches may form due to epistasis by an autosomal gene that shuts off pigment synthesis. A cat with colored patches against such a white background is a calico. Tortoiseshell and calico cats are nearly always female. A male can have these coat patterns only if he inherits an extra X chromosome.

In humans, X inactivation can be used to identify carriers of some X-linked disorders. This is the case for Lesch-Nyhan syndrome, in which an affected boy has cerebral palsy, bites his fingers, shoulders, and lips to the point of mutilation, is mentally retarded, and passes painful urinary stones. Mutation results in defective or absent HGPRT, an enzyme. A woman who carries Lesch-Nyhan syndrome can be detected when hairs from widely separated parts of her head are tested for HGPRT. (Hair is used for the test because it is accessible and produces the enzyme.) If some hairs contain HGPRT but others do not, she is a carrier. The hair cells that lack the enzyme have turned off the X chromosome that carries the normal allele;

the hair cells that manufacture the normal enzyme have turned off the X chromosome that carries the disease-causing allele. The woman is healthy because her brain has enough HGPRT, but each son has a 50 percent chance of inheriting the disease.

### Subtle Effects of X Inactivation

Theoretically, X inactivation evens out the sexes for expression of X-linked genes. In actuality, however, a female may *not* be equivalent, in gene expression, to a male because she has two cell populations, whereas a male has only one. One of a female's two cell populations has the X she inherited from her father active, and the other has the X chromosome she inherited from her mother active. For heterozygous X-linked genes, she would have some cells that manufacture the protein encoded by one allele, and some cells that produce the protein encoded by the other allele. Although most heterozygous genes have the alleles about equally represented, sometimes X inactivation can be skewed. That is, most cells express the X inherited from the same parent. This can happen if one of the X chromosomes includes an expressed allele that confers a greater rate of cell division than the different allele from the other parent, giving certain cells a survival advantage.

Another way that X inactivation makes a female different from a male, as far as X-linked gene expression is concerned, is revealed when the proteins encoded by different alleles interact. This can be beneficial or harmful. A beneficial example of dual expression of alleles occurs in certain types of monkeys in which an X-linked visual pigment gene has two alleles. Females who are homozygous for this gene and males have 2-color vision, but lucky female monkeys who are heterozygous for this gene enjoy 3-color vision.

A situation in which being a heterozygote for an X-linked gene is harmful is craniofrontonasal syndrome (OMIM 304110) (figure 6.14).

Males and homozygous females have asymmetrical facial features. However, heterozygous females have a much more severe phenotype, with very abnormal faces resulting from abnormal fusing of the skull bones. (It is highly unusual for the heterozygote to be more severely affected than the homozygous recessive individual.) An explanation is that the encoded protein is part of a signal transduction pathway that controls the bone fusion, and



**Figure 6.14** Craniofrontonasal syndrome is more severe in females because of an unusual detrimental effect of expressing both alleles of an X-linked gene.

down, depending upon whether the fertilized ovum chromosomally is male (XY) or female (XX). In this way, women can have sons and men can have daughters without passing on their sex-specific parental imprints.

The function of genomic imprinting isn't well understood, but because many imprinted genes take part in early development, it may be a way to finely regulate the amounts of key proteins in the embryo. The fact that some genes lose their imprints after birth supports this idea of early importance. Also, imprinted genes are in clusters along a chromosome, and are controlled by other regions of DNA called imprinting centers. Perhaps one gene in a cluster is essential for early development, and the others become imprinted simply because they are nearby—a bystander effect.

Genomic imprinting has implications for understanding early human development. It suggests that for mammals, it takes two opposite-sex parents to produce a healthy embryo and placenta. This apparent requirement for opposite-sex parents was discovered in the early 1980s, through experiments on early mouse embryos and examination of certain rare pregnancy problems in humans. Researchers created fertilized mouse ova that contained two male pronuclei or two female pronuclei, instead of one from each. Results were strange. When the fertilized ovum had two male genomes, a normal placenta developed, but the embryo was tiny and quickly stopped developing. A zygote with two female pronuclei, on the other hand, developed into an embryo, but the placenta was grossly abnormal. Therefore, the male genome controls placenta development, and the female genome, embryo development.

The mouse results were consistent with abnormalities of human development. When two sperm fertilize an oocyte and the female pronucleus degenerates, an abnormal growth of placenta-like tissue called a hydatidiform mole forms. If a fertilized ovum contains only two female genomes but no male genome, a mass of random differentiated tissue, called a teratoma, grows. A teratoma, which means “monster cancer,” may consist of a variety of tissues in a bizarre mix. With either a hydatidiform mole or a teratoma, no embryo results, although a pregnancy test may be positive, because the pregnancy hormone (hCG) may be produced.

Genomic imprinting can explain incomplete penetrance, in which an individual is known to have inherited a genotype associated with a particular phenotype, but has no signs of the trait—such as a person with normal fingers whose parent and child have polydactyly. An imprinted gene that silences the dominant mutant allele could explain these cases: The predicted genotype is present, but the associated phenotype is not expressed.

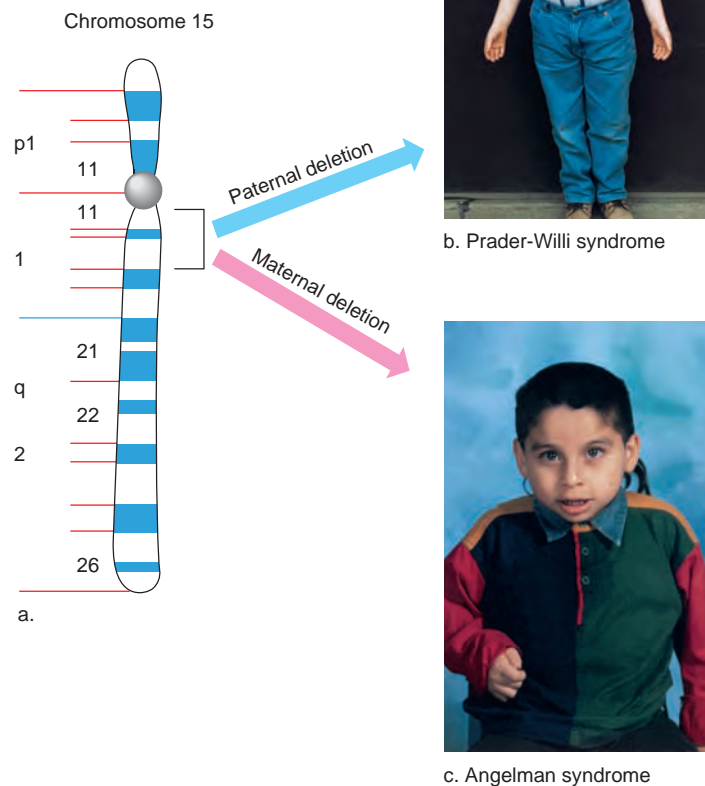
Imprinting may be an important concern in assisted reproductive technologies that manipulate gametes to treat infertility. For example, the otherwise very rare Angelman syndrome (OMIM 105830) and Beckwith-Wiedemann syndrome (OMIM 130650) are more prevalent among the offspring of people who used *in vitro* fertilization and

intracytoplasmic sperm injection (discussed in chapter 21) to become pregnant.

## Imprinting Disorders in Humans

At least 600 human genes are imprinted, and disruption of imprinting causes more than 30 known disorders. The effects of genomic imprinting are revealed only when an individual has one copy of a normally imprinted allele and the other, active allele is inactivated or deleted. This chapter concludes with compelling examples of the effects of genomic imprinting gone awry.

In humans, a striking example of genomic imprinting involves two different syndromes that arise from small deletions in the same region of chromosome 15 (**figure 6.17**). A child with Prader-Willi



**Figure 6.17 Prader-Willi and Angelman syndromes.** (a) Two distinct syndromes result from missing genetic material in the same region of chromosome 15. (b) Tyler has Prader-Willi syndrome, due to a deletion in the copy of the chromosome he inherited from his father. Note his small hands. (c) This child has Angelman syndrome, caused by a deletion in the chromosome 15 that he inherited from his mother. He is mentally retarded.

syndrome (OMIM 176270) is small at birth and in infancy has difficulty gaining weight. Between ages 1 and 3, the child develops an obsession with eating. Unless the diet can be controlled, severe obesity results because another symptom is a very slow metabolism. Parents actually lock kitchen cabinets and refrigerators to keep their children from literally eating themselves to death by bursting digestive organs. The other condition, Angelman syndrome, causes mental retardation, an extended tongue, large jaw, poor muscle coordination, and convulsions that make the arms flap. In many cases of Prader-Willi syndrome, only the mother's chromosome 15 region is expressed; the father's chromosome is deleted in that region. In Angelman syndrome, the reverse occurs: The father's gene (or genes) is expressed, and the mother's chromosome has the deletion.

Symptoms of Prader-Willi arise because several paternal genes that are not normally imprinted (that is, that are normally active)

are missing. In Angelman syndrome, a normally active single maternal gene is deleted. This part of chromosome 15 is especially unstable because it includes highly repetitive DNA sequences, which bracket the genes that cause the symptoms.

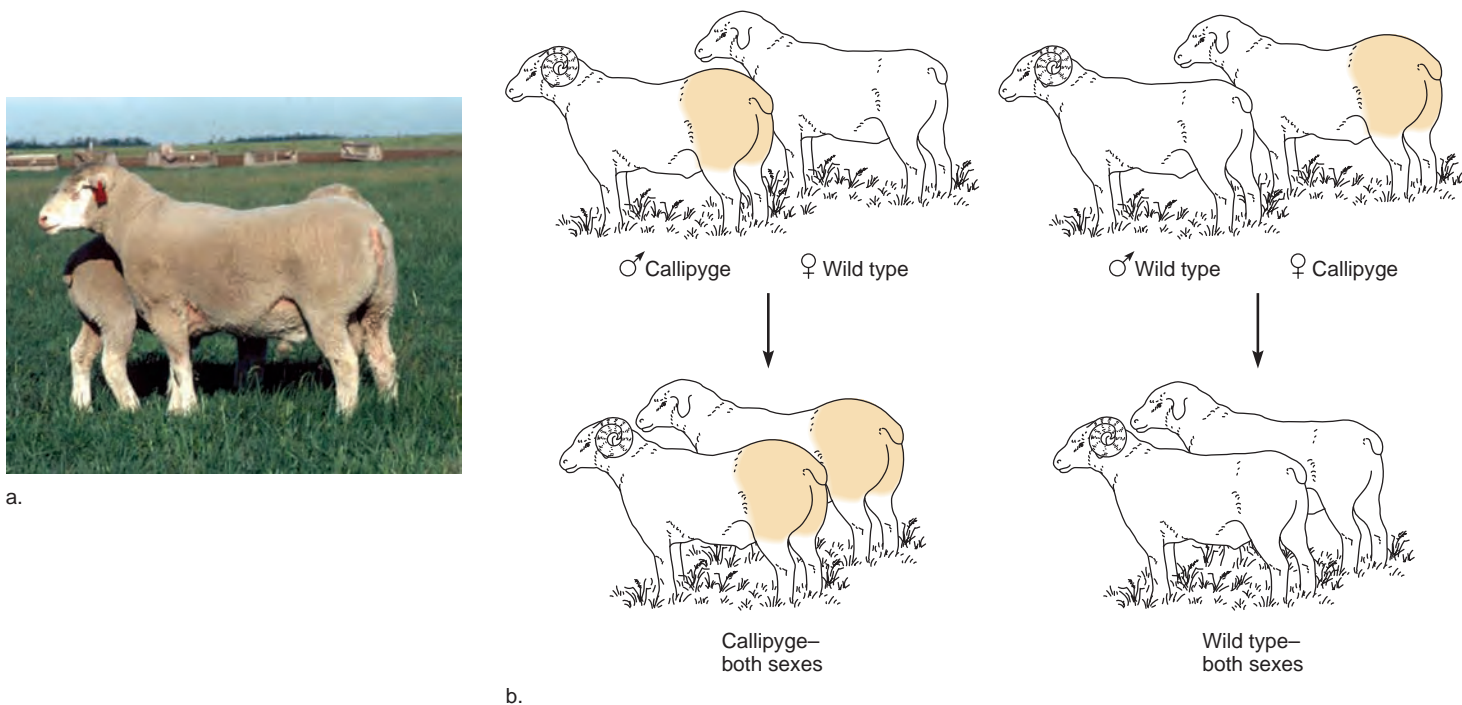
Imprinting gone awry is associated with forms of diabetes mellitus, autism, Alzheimer disease, schizophrenia, and male homosexuality. Clues that indicate a condition is associated with genomic imprinting include increased severity depending on whether it is inherited from the father or mother and also a phenomenon called **uniparental disomy**. This term literally means “two bodies from one parent,” and refers to an offspring who inherits both copies of a gene from one parent and none from the other. (Chapter 13 discusses uniparental disomy further.)

## A Sheep With a Giant Rear End

Genomic imprinting is easier to observe in species that can be bred, so that traits

can be followed over several generations. This is the case for Solid Gold, a ram with an overmuscled rear end (**figure 6.18a**), and his many offspring. Solid Gold was born in 1983 in Oklahoma, and by three weeks of age, his hefty hindquarters were attracting attention. With visions of extra-meaty lamb chops, the breeder, instead of shipping Solid Gold to market, mated him to see if the trait was inherited. Sure enough, at three weeks of age, some of the lambs started to grow giant rears. Solid Gold became a favorite in the show ring. When a biology graduate student in search of a research project became interested in him, the ram's story continued in the genetics journals. Researchers named the mutation *callipyge*, which is Greek for “beautiful buttocks.”

The trait was autosomal dominant, but people who tried to breed a stock from Solid Gold's lambs ran into a problem. The sheep seemed to be resisting Mendel's first law—the trait was passed only if it came from the father! In other words, a callipyge ewe did



**Figure 6.18 Genomic imprinting in a sheep's rear.** (a) Solid Gold astounded breeders with his overly muscled hindquarters. (b) Only callipyge males can pass on the trait, and only if the ewe is wild type.



not yield a callipyge lamb (**figure 6.18b**). The situation turned out to be even more complex than straight genomic imprinting—not only must the ram be callipyge, but the ewe must be wild type to transmit the trait to all offspring.

Researchers eventually identified the callipyge gene, and also discovered that when it is overexpressed in the big-reared sheep, so are seven neighboring genes on sheep chromosome 18. (These other genes control wool quality and which muscles overgrow.) The involvement of several genes

was another clue pointing to imprinting, which can affect a chromosome segment as well as an individual gene. Other researchers traced the entire suite of silenced genes to a single DNA base change, which disrupts imprinting.

Alas, the curious callipyge mutation did not turn out to be valuable to breeders—the meat was tough. However, callipyge genes were found in humans, inspiring magazine articles on the ability to inherit a large rear end.

## Key Concepts

1. In genomic imprinting, the phenotype differs depending on whether a gene is inherited from the mother or the father.
2. Methyl groups may bind to DNA and temporarily suppress gene expression in a pattern determined by the individual's sex.
3. Imprinting may be a normal process in mammalian embryos.

## Summary

### 6.1 Sexual Development

1. Sexual identity includes sex chromosome makeup; gonadal specialization; phenotype (reproductive structures); and gender identity.
2. The human male is the **heterogametic sex**, with an X and a Y chromosome. The female, with two X chromosomes, is the **homogametic sex**.
3. The human Y chromosome includes two **pseudoautosomal regions** and a large, male-specific region that does not recombine. Y-linked genes may correspond to X-linked genes, be similar to them, or be unique. Palindromic DNA sequences or inverted repeats can promote gene loss on the Y.
4. If the *SRY* gene is expressed, undifferentiated gonads develop as testes. If *SRY* is not expressed, the gonads develop as ovaries, under the direction of other genes.
5. Starting about eight weeks after fertilization, sustentacular cells in the testes secrete anti-Müllerian hormone, which prevents development of female structures, and interstitial cells produce testosterone, which triggers development of the epididymides, ductus deferentia, seminal vesicles, and ejaculatory ducts.
6. Testosterone converted to DHT controls development of the urethra, prostate gland, penis, and scrotum. If *SRY* is not

turned on, the Müllerian ducts continue to develop into female reproductive structures.

7. Evidence points to an inherited component to homosexuality.
8. **Sex ratio** is the number of males divided by the number of females multiplied by 1,000, for people of a particular age. Sex ratios are skewed by interfering with pregnancy outcomes. Exposure to violence and diseases that affect men more than women contribute to a sex ratio that favors women in the later years.

### 6.2 Traits Inherited on Sex Chromosomes

9. Y-linked traits are rare and are passed from fathers to sons only.
10. Males are **hemizygous** for genes on the X chromosome and express phenotypes associated with these genes because they do not have another allele on a homolog. An X-linked trait passes from mother to son because he inherits his X chromosome from his mother and his Y chromosome from his father.
11. An X-linked allele may be dominant or recessive. X-linked dominant traits are more devastating to males than to females.

### 6.3 Sex-Limited and Sex-Influenced Traits

12. **Sex-limited traits** may be autosomal or sex-linked, but they only affect one sex because of anatomical or hormonal gender differences.
13. A **sex-influenced gene** is dominant in one sex but recessive in the other.

### 6.4 X Inactivation

14. **X inactivation** shuts off one X chromosome in each cell in female mammals, making them mosaics for heterozygous genes on the X chromosome. This phenomenon evens out the dosages of genes on the sex chromosomes between the sexes.
15. A female who expresses the phenotype corresponding to an X-linked gene she carries is a **manifesting heterozygote**.

### 6.5 Genomic Imprinting

16. In **genomic imprinting**, the phenotype corresponding to a particular genotype differs depending on whether the parent who passes the gene is female or male.
17. Imprints are erased during meiosis and reassigned based on the sex of a new individual.
18. Methyl groups that temporarily suppress gene expression are the physical basis of genomic imprinting.

# Review Questions

1. How is sex expressed at the chromosomal, gonadal, phenotypic, and gender identity levels?
2. How do genes in the pseudoautosomal region of the Y chromosome differ from genes in the male-specific region (MSY)?
3. What are the phenotypes of the following individuals?
  - a. a person with a mutation in the *SRY* gene, rendering it nonfunctional
  - b. a normal XX individual
  - c. an XY individual with a block in testosterone synthesis
4. List the events that must take place for a fetus to develop as a female.
5. Cite evidence that may point to a hereditary component to homosexuality.
6. Why is it unlikely one would see a woman who is homozygous for an X-linked dominant condition?
7. What is the basis of sex ratio at birth?
8. Traits that appear more frequently in one sex than the other may be caused by genes that are inherited in an X-linked, sex-limited, or sex-influenced fashion. How might you distinguish among these possibilities in a given individual?
9. Why are male calico cats very rare?
10. How might X inactivation cause patchy hairiness on women who have congenital generalized hypertrichosis, even though the disease-causing allele is dominant?
11. How does X inactivation even out the “doses” of X-linked genes between the sexes?
12. Cite evidence that genetic contributions from both parents are necessary for normal prenatal development.
13. Prader-Willi and Angelman syndromes are more common in children conceived with certain assisted reproductive technologies (*in vitro* fertilization and intracytoplasmic sperm injection) than among the general population. What process may these procedures disrupt?

# Applied Questions

1. To answer the following questions, consider these population data on sex ratios:

Selected sex ratios at birth      Selected sex ratios after age 65

Nation	Sex ratio	Nation	Sex ratio
Costa Rica	970	Rwanda	620
Tanzania	1,000	South Africa	630
Liechtenstein	1,010	France	700
South Africa	1,020	United States	720
United States	1,050	Qatar	990
Sweden	1,060	Montserrat	1,060
Italy	1,070	Bangladesh	1,160
China	1,130	Nigeria	990

- a. In Rwanda, South Africa, France, and the U.S., males die, on average, significantly younger than females. What types of questions might you ask, or what types of statistics might you seek, to explain the difference?
  - b. In Costa Rica, how many males at birth are there for every 100 females?
  - c. In which country listed do males tend to live the longest?
2. In Hunter syndrome, lack of the enzyme iduronate sulfate sulfatase leads to buildup of carbohydrates called mucopolysaccharides. In severe cases, the liver, spleen, and heart swell. In mild cases, deafness may be the only symptom. Intellect is usually unimpaired, and life span can be normal. Hunter syndrome is X-linked recessive. Suppose a man who has mild Hunter syndrome has a child with a woman who is a carrier for the disorder.

- a. What is the probability that a son would inherit Hunter syndrome?
  - b. What is the chance that a daughter would inherit Hunter syndrome?
  - c. What is the chance that a daughter would be a carrier?
3. Amelogenesis imperfecta (OMIM 301200) is an X-linked dominant condition that affects tooth enamel. Affected males have extremely thin enamel layers all over each tooth. Female carriers have grooved teeth from the uneven deposition of enamel. Why might the phenotype differ between the sexes?

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, Chapter 6** and **Web Activities** to find the website links needed to complete the following activities.

4. Visit the National Center for Biotechnology Information (NCBI) website. Identify an X-linked disorder, then find it in OMIM and describe it.
5. At the Imprinted Gene Catalogue website, click on “search by species name” and then click on “complete list.” Find two disorders that involve imprinting, one transmitted from the mother and one from the father, and use OMIM to describe them.

## Case Studies and Research Results

6. For each case description, identify the principle at work from the list that follows. More than one answer per case may apply.
  - A. Y-linked inheritance
  - B. X-linked recessive
  - C. X-linked dominant inheritance
  - D. Sex-limited inheritance
  - E. Sex-influenced inheritance
  - F. X inactivation or manifesting heterozygote
  - G. Uniparental disomy
  - H. Imprinting abnormality
- a. In a well-studied three-generation family, sixteen members have speech-language disorder (OMIM 602081). Affected individuals cannot speak. The gene that causes the disorder is called *FOXP2*. The speechless members of this family inherited both copies of the gene from their mothers and have none from their fathers.
- b. Six-year-old LeQuan inherited Fabry disease (301500) from his mother, who is a heterozygote for the causative mutation. The gene, located on the X chromosome, encodes a lysosomal enzyme. LeQuan would die before age 50 of heart failure, kidney failure, or a stroke, but fortunately his condition

# A Second Look

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1. What is the risk that a sister of one of the three little boys who died of WAS in the originally studied family had:
  - a. a son with WAS
  - b. a healthy son
  - c. a daughter who was/is a carrier of WAS
2. If the boy treated with the stem cell transplant has a son with a woman who does not have WAS in her family, what is the risk that he will inherit WAS?

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

Anhidrotic ectodermal dysplasia  
Blue diaper syndrome  
Chronic granulomatous disease  
Congenital muscular dystrophies  
Intersex



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.



# Multifactorial Traits

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- 7.1 **Genes and the Environment Mold Most Traits**
  - Polygenic Traits Are Continuously Varying
  - Fingerprint Patterns
  - Height
  - Eye Color
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- 7.2 **Investigating Multifactorial Traits**
  - Empiric Risk
  - Heritability
  - Adopted Individuals
  - Twins
  - Association Studies
- 7.3 **Two Multifactorial Traits**
  - Heart Health
  - Weight

## CLEFT LIP AND PALATE

The young couple was shocked when they first saw their daughter. She had a cleft lip and palate—a hole between her nose and upper lip. The parents soon discovered that feeding Emily was difficult, because she could not maintain suction. Special nipples on her bottles helped.

Today, Emily is 14, and has a glorious smile. The defect occurred between weeks 4 and 12 of prenatal development, when her nose and jaw failed to meet and close. Emily had several surgeries. Her first procedure, at 4 months, repaired her lip; the second, at a year, connected the edges of her palate (the roof of the mouth) and repositioned tissue at the back of her throat to correct her nasal speech. A speech and language therapist helped with Emily's early feeding problems and assisted her when frequent ear infections, due to openings at the back of her throat, caused hearing loss. At age seven Emily had orthodontia to make room for her permanent teeth, and at age 10, bone from her hip was used to strengthen her palate so that it could support teeth. At age 16, Emily can have surgery on her nose to build it up and straighten it.

Cleft lip, with or without cleft palate, is very variable in severity and has genetic and environmental components. Known causes include prenatal exposure to certain drugs used to treat seizures, anxiety, and high cholesterol; pesticide residues; cigarette smoke; and infections. Emily's parents were nervous when expecting their second child, because population data indicated that the risk that he would be affected was about 4 percent. He wasn't. Today, tests can detect specific haplotypes associated with elevated risk of developing cleft lip and/or palate.

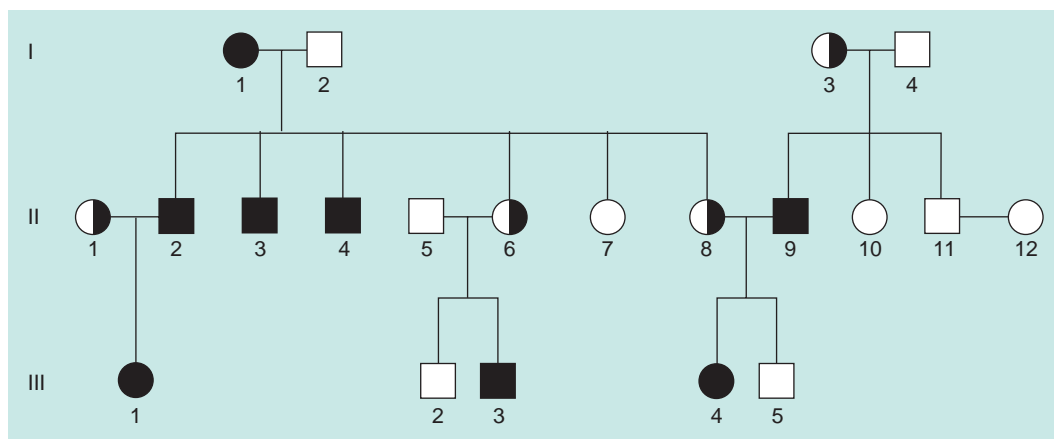


Cleft lip is more likely to occur in a person who has a relative with the condition. This child has had corrective surgery.

- can be treated with twice-monthly infusions of the enzyme that his body cannot produce. His mother, Echinecea, has been well until recently, when she began experiencing recurrent fevers, a burning pain in her hands and feet, a rash, and sensitivity to cold temperatures. A geneticist tells her that she is experiencing mild symptoms of Fabry disease, because the normal allele is turned off in certain cells that are affected by the symptoms.
- The Chandler family has many male members who have a form of retinitis pigmentosum, in which the cells that capture light energy in the retina degenerate, causing gradual visual loss. Several female members of the family presumed to be carriers because they have affected sons are tested for RP genes on chromosomes 1, 3, 6, and the X, but do not carry these RP genes. Many years ago, Rachel married her cousin Ross, who has the family's form of RP. They had six children. The three sons are all affected, but their daughters all have normal vision.
  - Simon's mother and her sister are breast cancer survivors, and their mother died of the disease. Simon's sister Maureen has a genetic test and learns that she, too, has inherited the *BRCA1* gene. Simon has two daughters, but doesn't want to be tested because he thinks a man cannot transmit a trait that affects a body part that is more developed in females. His sisters convince him otherwise. He has the test.
  - Tribbles are extraterrestrial mammals that long ago invaded a star ship on the television program *Star Trek*. A gene called *frizzled* causes kinky hair in female tribbles who inherit just one allele. However, two mutant alleles must be inherited for a male tribble to have kinky hair.
  - Prozac died at age 16 of Lowe syndrome (OMIM 309000). He was slightly mentally retarded, had visual problems (cataracts and glaucoma), seizures, poor muscle tone, and progressive kidney failure, which was ultimately fatal. His sister Lunesta is pregnant, and wonders whether she is a carrier of the disease that killed her brother. She remembers a doctor saying that her mother Yaz was a carrier. Lunesta's physician determines that she is a carrier because she has cataracts,

which is a clouding of the lenses. It has not yet affected her vision. When a prenatal test reveals that Lunesta's fetus is a female, her doctor tells her not to worry about Lowe syndrome.

- Mating among Texas field crickets depends upon females responding to a male mating call. The sounds must arrive at a particular frequency to excite the females, who do not sing back in response. However, females can pass on a trait that confers frequency of singing.
  - When Winthrop was a baby, he was diagnosed with "failure to thrive," a general term that can be applied to many medical conditions that prevent an infant from gaining sufficient weight. Then, at 14 months of age, Winthrop suddenly took an interest in food, and his parents couldn't feed him fast enough. They were proud when he'd finish his meal and want more. But by age 4, Winthrop was obese, and his parents became disturbed at his behavior. He was so hungry that after he'd eaten his meal and everyone else's leftovers, he'd hunt through the garbage for more. Once his mother had even found him rooting around the neighbor's garbage can. They finally took him to a psychiatrist who had a background in genetics, and Prader-Willi syndrome was diagnosed. Testing showed that the allele for the Prader-Willi gene that Winthrop had inherited from his father was abnormally methylated.
  - Certain breeds of dogs have cryptorchidism, in which the testicles do not descend into the scrotum. The trait is passed through females, even though they cannot express it.
- Reginald has mild hemophilia A that he can control by taking a clotting factor. He marries Lydia, whom he met at the hospital where he and Lydia's brother, Marvin, receive their treatment. Lydia and Marvin's mother and father, Emma and Clyde, do not have hemophilia. What is the probability that Reginald and Lydia's son will inherit hemophilia A?
  - Harold works in a fish market, but the odor does not bother him because he has anosmia (OMIM 301700), an X-linked recessive lack of sense of smell. Harold's wife, Shirley, has a normal sense of smell. Harold's sister, Maude, also has a normal sense of smell, as does her husband, Phil, and daughter, Marsha, but their identical twin boys, Alvin and Simon, cannot detect odors. Harold and Maude's parents, Edgar and Florence, can smell normally. Draw a pedigree for this family, indicating people who must be carriers of the anosmia gene.
  - Metacarpal 4–5 fusion is an X-linked recessive condition in which certain finger bones are fused. It occurs in many members of the Flabudgett family, depicted in the pedigree at the bottom of the page.
    - Why are three females affected, considering that this is an X-linked condition?
    - What is the risk that individual III-1 will have an affected son?
    - What is the risk that individual III-5 will have an affected son?
  - Herbert is 58 years old and bald. His wife, Sheri, also has pattern baldness. What is the risk that their son, Frank, will lose his hair?



Metacarpal 4–5 fusion

A woman who is a prolific writer has a daughter who becomes a successful novelist. An overweight man and woman have obese children. A man whose father suffers from alcoholism has the same problem. Are these characteristics—writing talent, obesity, and alcoholism—inherited or learned? Or are they a combination of nature (genetics) and nurture (the environment)?

Most of the traits and medical conditions mentioned so far in this book are single-gene characteristics, inherited according to Mendel's laws, or linked on the same chromosome. Many single-gene disorders are very rare, each affecting one in hundreds or even thousands of individuals. Using Mendel's laws, geneticists can predict the probability that certain family members will inherit single-gene conditions. Most more common traits and diseases, though, seem to “run in families” with no obvious pattern, or they occur sporadically, with just one case in a family.

Genes rarely act completely alone. Even single-gene disorders are modified by environmental factors and/or other genes. This chapter discusses non-Mendelian characteristics, and the tools used to study them. Chapter 8 focuses on the most difficult traits to assess for their inherited components—those that affect the nervous system, including behavioral disorders.

## 7.1 Genes and the Environment Mold Most Traits

On the first page of the first chapter of *On the Origin of Species*, Charles Darwin noted that two factors are responsible for biological variation—“the nature of the organism and the nature of the conditions.” Darwin's thoughts were a nineteenth-century musing on heredity versus the environment. Though this phrase might seem to indicate that genes and the environment are adversaries, they are actually two forces that interact, and they do so in ways that mold many of our characteristics.

A trait can be described as either single-gene (or Mendelian or monogenic) or **polygenic**. As its name implies, a polygenic

trait reflects the activities of more than one gene. Both single-gene and polygenic traits can also be **multifactorial**, which means they are influenced by the environment. Pure polygenic traits—those not influenced by the environment—are very rare.

Multifactorial traits affect more than 1 in 1,000 individuals and include height, skin color, body weight, illnesses, and behavioral conditions and tendencies. Behavioral traits are not inherently different from other types of traits; they involve the functioning of the brain, rather than another organ. A more popular term for “multifactorial” is complex, but we use multifactorial here because it is more precise and is not confused with the general definition of “complex.” The genes of a multifactorial trait are not inherently more complicated than others. They follow Mendel's laws, but expression of the genes is more difficult to predict because of the combined actions of genes and the environment.

An example of a single-gene trait that is influenced by the environment is alpha-1 antitrypsin (AAT) deficiency (OMIM 107400), which causes an inherited form of the lung disease emphysema. Although some individuals who inherit AAT deficiency develop lung problems early in life even if they never smoke or encounter pollution, others require exposure to an irritant to become ill. People with AAT deficiency were overrepresented among the rescue workers from the World Trade Center site on September 11, 2001 who developed persistent lung problems. Exposure to the particle-laden air at the site triggered or hastened their inherited lung disease.

A polygenic multifactorial condition reflects additive contributions of several genes. Each gene confers a degree of susceptibility, but the input of these genes is not necessarily equal. For example, three genes contribute to the risk of developing type 2 diabetes mellitus.

Different genes may contribute different aspects of a phenotype that was once thought to be due to the actions of a single gene. Consider migraine, a condition for which many a sufferer will attest is more than just a headache. Studies have found that a gene on chromosome 1 contributes

sensitivity to sound; a gene on chromosome 5 produces the pulsating headache and sensitivity to light; and a gene on chromosome 8 is associated with nausea and vomiting. In addition, certain environmental influences are well known to trigger migraine in some people. Migraine is a very complex complex trait!

## Polygenic Traits Are Continuously Varying

For a polygenic trait, the combined action of many genes often produces a “shades of grey” or “continuously varying” phenotype, also called a quantitative trait. DNA sequences that contribute to polygenic traits are called **quantitative trait loci**, or QTLs. A multifactorial trait is continuously varying if it is also polygenic. That is, it is the multi-gene component of the trait that contributes the continuing variation of the phenotype. The individual genes that confer a polygenic trait follow Mendel's laws, but together they do not produce single-gene phenotypic ratios. They all contribute to the phenotype, but without being dominant or recessive to each other. For example, the multiple genes that regulate height and skin color result in continuously varying phenotypes. Single-gene traits are instead discrete or qualitative, often providing an “all-or-none” phenotype such as “normal” versus “affected.”

A polygenic trait varies in populations, as our many nuances of hair color, body weight, and cholesterol levels demonstrate. Some genes contribute more to a polygenic trait than others. Within genes, alleles can have differing impacts depending upon exactly how they alter an encoded protein and how common they are in a population. For example, a mutation in the gene that encodes the receptor that takes LDL cholesterol into cells drastically raises blood serum cholesterol level. But because fewer than 1 percent of the individuals in most populations have this mutation, it contributes very little to the variation in cholesterol level at the population level.

Although the expression of a polygenic trait is continuous, we can categorize individuals into classes and calculate the frequencies of the classes. When we do this



and plot the frequency for each phenotype class, a bell-shaped curve results. Even when different numbers of genes affect the trait, the curve takes the same shape, as is evident in the following examples.

## Fingerprint Patterns

The skin on the fingertips is folded into patterns of raised skin called dermal ridges that align to form loops, whorls, and arches. This pattern is a fingerprint. A technique called dermatoglyphics (“skin writing”) compares the number of ridges that comprise these patterns to identify and distinguish individuals (**figure 7.1**). Dermatoglyphics is part of genetics because certain disorders (such as Down syndrome) include unusual ridge patterns. Forensic fingerprint analysis is also dermatoglyphics.

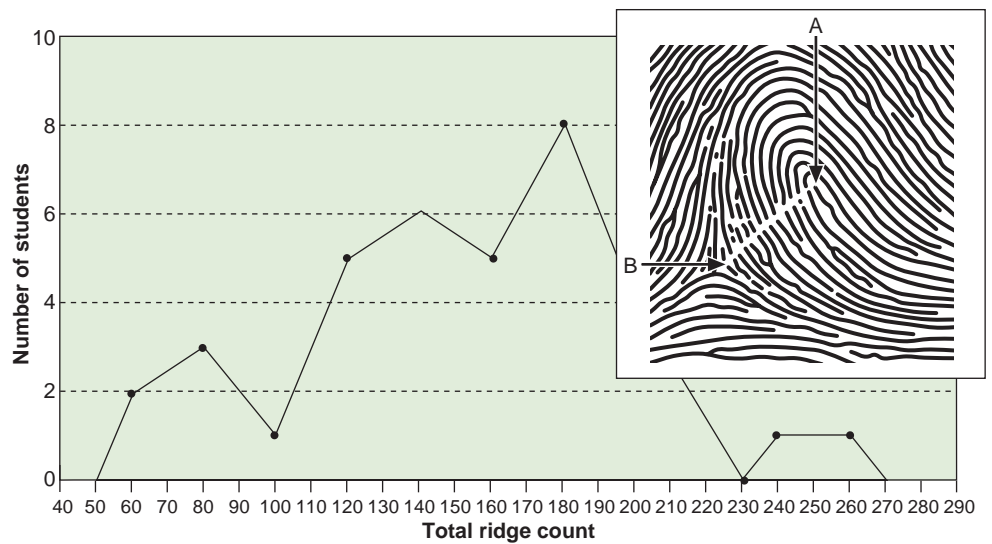
The number of ridges in a fingerprint is largely determined by genes, but also responds to the environment. Therefore it is multifactorial. During weeks 6 through 13 of prenatal development, the ridge pattern can be altered as the fetus touches the finger and toe pads to the wall of the amniotic sac. This early environmental effect explains why the fingerprints of identical twins, who share all genes, are in some cases not exactly alike.

We can quantify a fingerprint with a measurement called a total ridge count, which tallies the numbers of ridges in whorls, loops, or arches. The average total ridge count in a male is 145, and in a female, 126. Plotting total ridge count reveals the bell curve of a continuously varying trait.

## Height

The effect of the environment on height is obvious—people who do not eat enough do not reach their genetic potential for height. Students lined up according to height, but raised in two different decades and under different circumstances, vividly reveal the effects of genes and the environment on this continuously varying trait. Part *a* of **figure 7.2** depicts students from 1920, and part *b*, students from 1997. But also note that the tallest people in the old photograph are 5'9", whereas the tallest people in the more recent photograph are 6'5". The difference is attributed to improved diet and better overall health.

We usually do not know exactly how many genes contribute to multifactorial traits that are also polygenic. However,



**Figure 7.1 Anatomy of a fingerprint.** Total ridge counts for a number of individuals, plotted on a bar graph, form an approximate bell-shaped curve. The number of ridges between landmark points A and B on this loop pattern is 12. Total ridge count includes the number of ridges on all fingers.

Data and print from Gordon Mendenhall, Thomas Mertens, and Jon Hendrix, “Fingerprint Ridge Count,” in *The American Biology Teacher*, vol. 51, no. 4, April 1989, pp. 204–6. American Biology Teacher by Medenhall, Mertens, and Hendrix. Copyright 1989 by National Association of Biology Teachers. Reproduced with permission of National Association of Biology Teachers in the format via Copyright Clearance Center.



**a.**



**b.**

**Figure 7.2 The inheritance of height.** The photograph in (**a**) illustrates the continuously varying nature of height. In the photo, taken around 1920, 175 cadets at the Connecticut Agricultural College lined up by height. (**b**) In 1997, professor Linda Strausbaugh asked her genetics students at the school (today the University of Connecticut at Storrs) to re-create the scene.

geneticists can suggest models for a certain number of genes contributing to a trait based on the number of variants that can be discerned—although this is limited by what we can detect.

## Eye Color

Eye color is probably a pure polygenic trait—one with no environmental input (colored contact lenses don't count). But eye color isn't only a matter of brown, blue, green, or hazel. Overlying the common tones are specks and flecks, streaks and rings, and regions of dark versus light. These modifications arise from the way pigment is laid down onto the distinctive peaks and valleys at the back of the iris, the colored portion of the eye.

Two genes specify greenish-blue pigments called lipochromes, and two or more other genes encode the brownish melanins. These genes interact in a hierarchy, with the brown genes masking the green/blues, and everything masking pure blue. Unlike the browns, which are caused by chemical pigments, pure blue is a "spectral color" that results from light scattering, much as the blue of the sky is an effect of the sun's rays

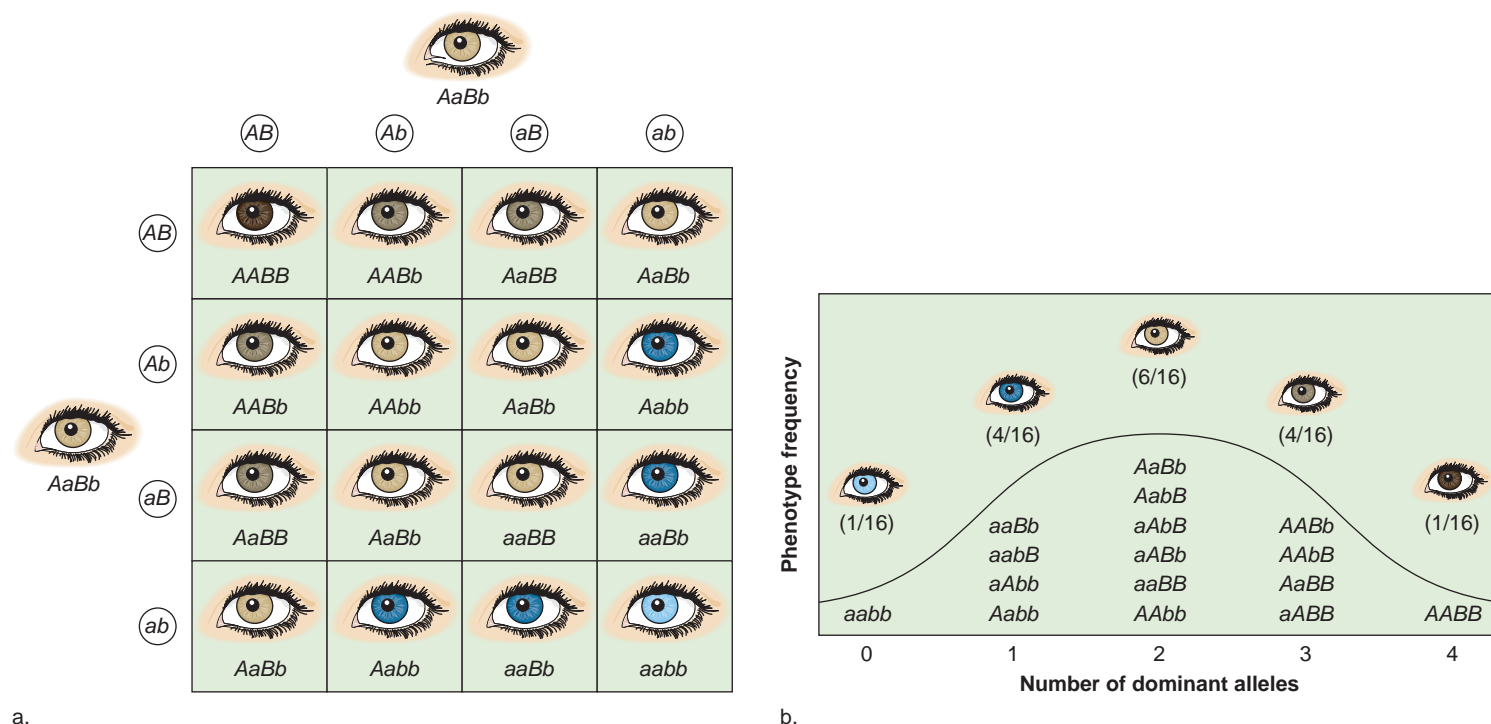
penetrating the atmosphere. Hazel eyes have a mixture of lipochromes and melanins. Blue-eyed parents can have brown-eyed children if the parents do not have pure blue eyes—which few people do. Each parent contributes a slight ability to produce pigment, which adds in the child to color the irises a pale brown. Unlike pigment in the skin, melanin in the iris stays in the cell that produces it.

The topography at the back of the iris is as distinctive as fingerprints, and is an inherited trait. Thicker parts of this area darken the appearance of the pigments, rendering brown eyes nearly black in some parts, or blue eyes closer to purple. The bluest of blue eyes have thin irises with very little pigment. The effect of the iris surface on color is a little like the visual effect of a rough-textured canvas on paint.

For many years, eye color was thought to arise from two genes with two alleles each, as depicted in **figure 7.3**. Although this is a gross oversimplification, it does illustrate the bell curve that describes the phenotypes resulting from gene interaction. These alleles interact additively to produce five eye colors—light blue, deep blue or green, light brown, medium brown,

and dark brown/black. If each allele contributes a certain amount of pigment, then the greater the number of such alleles, the darker the eye color. If eye color is controlled by two genes, *A* and *B*, each of which comes in two allelic forms—*A* and *a* and *B* and *b*—then the lightest color would be genotype *aabb*; the darkest, *AABB*. The bell curve arises because there are more ways to inherit light brown eyes, the mid-range color, with any two contributing dominant alleles, than there are ways to inherit the other colors.

Analysis of the human genome will likely reveal additional eye color genes—the mouse has more than 60! Recognizing that there may be dozens of variations of eye color, with distinctions perhaps beyond our perception, one company has analyzed 300 sites within the two lipochrome and two melanin genes in hundreds of individuals. From this information, their researchers have developed a forensic tool called the "retinome," which is a database of eye color gene variants that goes well beyond the standard four that appear on a driver's license. Using the retinome, a criminal suspect's eye color can be determined from a single cell of evidence.



**Figure 7.3 Variations in eye color.** (a) A model of two genes, with two alleles each, can explain the existence of five eye colors in humans. (b) The frequency distribution of eye colors forms the characteristic bell-shaped curve for a polygenic trait.

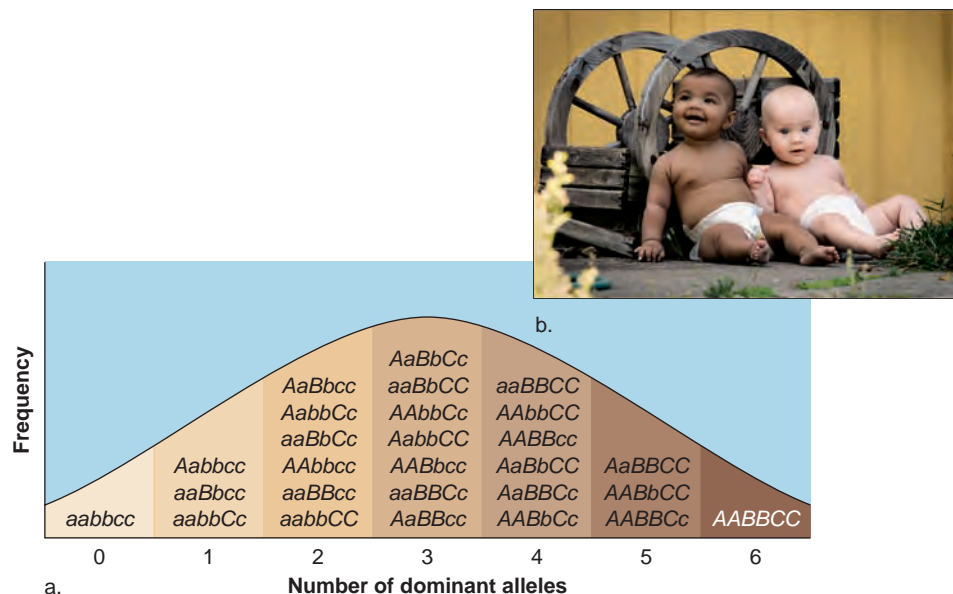
## Skin Color

Melanin pigment colors the skin to different degrees in different individuals. In the skin, cells called melanocytes contain melanin within lipid-bounded organelles called melanosomes. Melanocytes extend between tile-like skin cells, distributing pigment granules through the skin layers. Some melanin exits the melanocytes and enters the hardened cells in the skin's upper layers. Here the melanin breaks into pieces, and as the skin cells are pushed up toward the skin's surface, the melanin bits provide color. The pigment protects against DNA damage from ultraviolet radiation, and exposure to the sun increases melanin synthesis. **Figure 7.4** shows a three-gene model for human skin color—an oversimplification of this highly variable trait.

Although people come in a wide variety of hues, we all have about the same number of melanocytes per unit area of skin. However, people differ in melanosome number, size, and density of distribution. Differences in skin color arise from the number and distribution of melanin pieces in the skin cells in the uppermost layers. People with a single-gene condition called albinism cannot manufacture melanin (see figure 4.15). There are several types of albinism, indicating that several genes contribute to skin color.

A major genetic determinant of skin color was recently discovered in humans, based on a mutation called “golden” in zebrafish. This animal is often used in research because its embryos are transparent, so early development can be observed. The mutant fish are light in color. Researchers used the known sequence of the fish color gene to identify its counterpart in the human genome. African and East Asian human populations have a different variant of this gene than white European populations. The evidence that humans have had a hand in determining skin color, via selection, is discussed in chapter 16.

Skin color is one trait used to distinguish race. However, the definition of race based largely on skin color is more a social construct than a biological concept, for skin color is but one of thousands of traits whose frequencies vary in different populations. From a genetic perspective, when referring to other types of organisms, races are



**Figure 7.4 Variations in skin color.** (a) A model of three genes, with two alleles each, can explain broad hues of human skin. In actuality, this trait likely involves many more than three genes. (b) Humans come in a great variety of skin colors. Skin color genes can sort themselves out in interesting ways. These beautiful young ladies, Alicia and Jasmin, are twins! Their father is German and their mother is Jamaican-English.

groups within species that are distinguished by different allele frequencies. Humans are actually a lot less variable in appearance than other mammals, although it may seem to us that all chimps look alike. Although we tend to classify people by skin color because it is an obvious visible way to distinguish individuals, skin color is not a reliable indicator of ancestry.

When many genes are considered, two people with black skin may be less alike than either is to another person with white skin. For example, sub-Saharan Africans and Australian aborigines have dark skin, but are very dissimilar in other inherited characteristics. Their dark skins may reflect adaptation to life in a sunny, tropical climate rather than recent shared ancestry. Overall, 93 percent of varying inherited traits are no more common in people of one skin color than any other.

In one telling investigation, 100 students in a sociology class in “Race and Ethnic Relations” at Pennsylvania State University demonstrated that skin color does not necessarily reflect ancestry. The students had their DNA tested for percent contribution from “European white,” “black African,” “Asian,” and “Native American” gene variants that are more common in these groups. No student was pure anything, and

many were quite surprised at what their DNA revealed about their ancestry. One student, a light-skinned black, learned that genetically he is 52 percent black African and 48 percent European white: approximately half black, half white. Another student who considered herself black was actually 58 percent white European. The U.S. census, in recognition of the complexity of classifying people into races based on skin color, began to allow “mixed race” as a category in 2000. Many of us fall into this category.

Although in a genetic sense the concept of race based on skin color has little meaning, in a practical sense, such groups do have different incidences of certain diseases. This reflects the tendency to choose partners within the group, which retains certain alleles. However, racial differences in disease prevalence may also result from social inequities, such as some groups’ limited access to good nutrition or health care. Observations that members of particular races have a higher incidence of certain illnesses have influenced medical practice. The most widely publicized example of “race-based prescribing” is the marketing of certain hypertension and heart disease drugs to African Americans, who have a higher incidence of these conditions than



Table 7.1

## Different Drug Responses Among European Americans and African Americans

Researchers have compared the effects of many drugs in different racial or ethnic groups. Most drugs tested either show no difference, or do show a difference but the physiological basis isn't known. For some drugs, one group will tend to respond to lower doses or in greater numbers than another. Some of these drugs are listed here. The difference in response is associated with inheriting particular gene variants or SNPs. (EA stands for European American and AA stands for African American.)

Drug Class/Name	Disorder	More Effective In:	
		EA	AA
ACE inhibitor/Enalapril	hypertension	✓	
Antipsychotic/Clozapine	psychosis		✓
Antiviral/Alpha interferon	hepatitis	✓	
Beta blocker/Propranolol	hypertension	✓	
Calcium channel blocker/Diltiazem	hypertension		✓
Insulin	diabetes mellitus	✓	
Thiazide diuretic	hypertension		✓
Vasodilator combination/BiDil	congestive heart failure		✓

do people in other groups. **Table 7.1** lists some drugs that seem to be more effective among either Americans of European descent or Americans of African descent.

Offering medical treatments based on skin color may make sense on a population level, but on the individual level it may lead to errors, as the students at Penn State discovered when they learned how racially mixed they are. A white person might be denied a drug that would work, or a black person given one that doesn't, if the treatment decision is based on a superficial trait not directly related to how the body responds to a particular drug.

Genetics and genomics will address the problems inherent in race-based medicine by personalizing prescribing practices. The U.S. Food and Drug Administration published guidelines in 2005 for submission of data on correlations between genotypes and drug responses. Such data can reveal the bases of drug resistance and sensitivity. For example, in one study, researchers identified variants of a gene called *MDR* (for multi-drug resistance) in four population groups. This gene encodes a protein that pumps poisons out of certain white blood cells and intestinal lining cells. When a gene variant results in a pump that works too well, the protein recognizes drugs used to treat

cancer, AIDS, and other conditions as toxins, sending them out of the cell. Researchers have found this protein variant in 83 percent of West Africans, 61 percent of African Americans, 26 percent of Caucasians, and 34 percent of Japanese. MDR genotype could be used to prescribe certain drugs only for individuals whose cells would not pump the drugs out. Thus, MDR genotype is a more biologically meaningful basis for prescribing a drug than skin color.

In an even more compelling study, researchers cataloged 23 markers for genes that control drug metabolism in 354 people representing eight races: black (Bantu, Ethiopian, and Afro-Caribbean), white (Norwegian, Armenian, and Ashkenazi Jews), and Asian (Chinese and New Guinean). The genetic markers fell into four very distinct groups that predict which of several blood thinners, chemotherapies, and painkillers will be effective—and these response groups did not at all match the traditional racial groups.

The premises behind race-based prescribing are far more complex than black versus white. Although some genes and their variants are not distributed along racial lines, such as the 23 markers of drug metabolism just discussed, others apparently are. This is the case for a gene that

encodes an enzyme called leukotriene A4 hydrolase. The enzyme is necessary to produce leukotrienes, which inflame arteries as part of the immune response to infection. Excess leukotrienes increase the risk of heart attack. An allele present in European Americans and European populations for many years increases heart attack risk only slightly. Researchers hypothesize that enough time has passed that variants of other genes that temper the negative effects of excess leukotrienes have accumulated in these white groups. The overactive leukotriene A4 hydrolase allele, however, has only recently been introduced into the African American population. Without enough time for genetic protection to have arisen, the excess leukotrienes elevate risk of heart attack among African Americans five-fold compared to a mere 16 percent elevation among whites.

Basing medical decisions solely on race or ethnic group can lead to errors, such as failing to offer a drug that may be helpful to an individual who belongs to a group in which that drug does not usually work. However, on a population level, certain disorders *are* more prevalent in certain groups. Chapter 15 explores this stratification of human populations further.

## Key Concepts

1. Polygenic traits are determined by more than one gene and vary continuously in expression.
2. Multifactorial traits are determined by a combination of a gene or genes and the environment.
3. A bell curve describes the distribution of phenotypic classes of a polygenic trait.

## 7.2 Investigating Multifactorial Traits

It is much more challenging to predict recurrence risks for polygenic traits and disorders than for single-gene traits. Geneticists evaluate the input of genes, using information from population and family studies. In addition, the human genome sequence is providing new clues to multifactorial traits and disorders.

## Empiric Risk

Using Mendel's laws, it is possible to predict the risk that a single-gene trait will recur in a family if one knows the mode of inheritance—such as autosomal dominant or recessive. To predict the chance that a multifactorial trait will occur in a particular individual, geneticists use **empiric risks**, which are based on incidence in a specific population. **Incidence** is the rate at which a certain event occurs, such as the number of new cases of a particular disorder diagnosed per year in a population of known size. **Prevalence** is the proportion or number of individuals in a population who have a particular disorder at a specific time.

Empiric risk is not a calculation, but a population statistic based on observation. The population might be broad, such as an ethnic group or community, or genetically more well-defined, such as families that have a particular disease. Empiric risk increases with the severity of the disorder, the number of affected family members, and how closely related a person is to affected individuals. As an example, consider using empiric risk to predict the likelihood of a child being born with a neural tube defect (NTD). In the United States, the overall population risk of carrying a fetus with an NTD is about 1 in 1,000 (0.1 percent). For people of English, Irish, or Scottish ancestry, the risk is about 3 in 1,000. However, if a sibling has an NTD, no matter what the ethnic group, the risk of recurrence increases to 3 percent, and if two siblings are affected, the risk to a third child is even greater. By determining whether a fetus has any siblings with NTDs, a genetic counselor can predict the risk to that fetus, using the known empiric risk.

If a trait has an inherited component, then it makes sense that the closer the relationship between two individuals, one of whom has the trait, the greater the probability that the second individual has the trait, too, because they have more genes in common. Studies of empiric risk support this logic. **Table 7.2** summarizes empiric risks for relatives of individuals with cleft lip.

Because empiric risk is based solely on observation, we can use it to derive risks for disorders with poorly understood transmission patterns. For example, certain multifactorial disorders affect one sex more often than the other. Pyloric stenosis is an

**Table 7.2**

**Empiric Risk of Recurrence for Cleft Lip**

Relationship to Affected Person	Empiric Risk of Recurrence
Identical twin	40.0%
Sibling	4.1%
Child	3.5%
Niece/nephew	0.8%
First cousin	0.3%
General population risk (no affected relatives)	0.1%

overgrowth of muscle at the juncture between the stomach and the small intestine. It is five times more common among males than females. The condition must be corrected surgically shortly after birth, or the newborn will be unable to digest foods. Empiric data show that the risk of recurrence for the brother of an affected brother is 3.8 percent, but the risk for the brother of an affected sister is 9.2 percent. An empiric risk, then, is based on real-world observations—the mechanism of the illness or its cause need not be known.

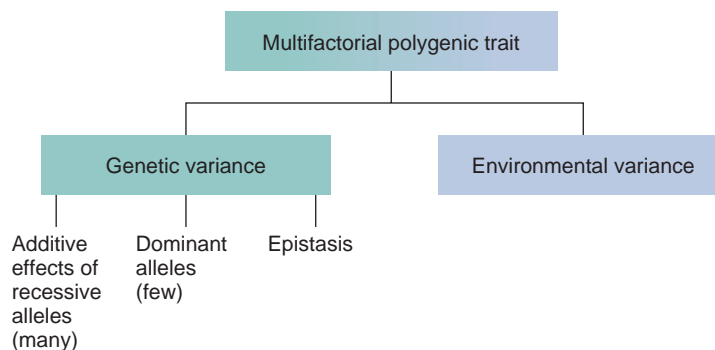
## Heritability

As Charles Darwin noted, some of the variation of a trait is due to inborn differences in populations, and some to differences in environmental influences. A measurement called **heritability**, designated  $H$ , estimates the proportion of the phenotypic variation for a particular trait that is due to genetic differences in a certain population

at a certain time. The distinction between empiric risk and heritability is that empiric risk could result from nongenetic influences, whereas heritability focuses on the genetic component of a trait.

**Figure 7.5** outlines the factors that contribute to observed variation in a trait. Heritability equals 1.0 for a trait whose variability is completely the result of gene action, such as in a population of laboratory mice whose environment is controlled. Without environmental variability, genetic differences determine expression of the trait in the population. Variability of most traits, however, reflects a combination of differences among genes and environmental components. **Table 7.3** lists some traits and their heritabilities.

Heritability changes as the environment changes. For example, the heritability of skin color would be higher in the winter months, when sun exposure is less likely to increase melanin synthesis. The same trait may be highly heritable in two populations,



**Figure 7.5** Heritability estimates the genetic contribution to a trait. Observed variance in a polygenic, multifactorial trait or illness reflects genetic and environmental contributions. Genetic variants are mostly determined by the additive effects of recessive alleles of different genes, but they can also be influenced by the effects of a few dominant alleles and by epistasis (interactions between alleles of different genes).

## Reading 7.1

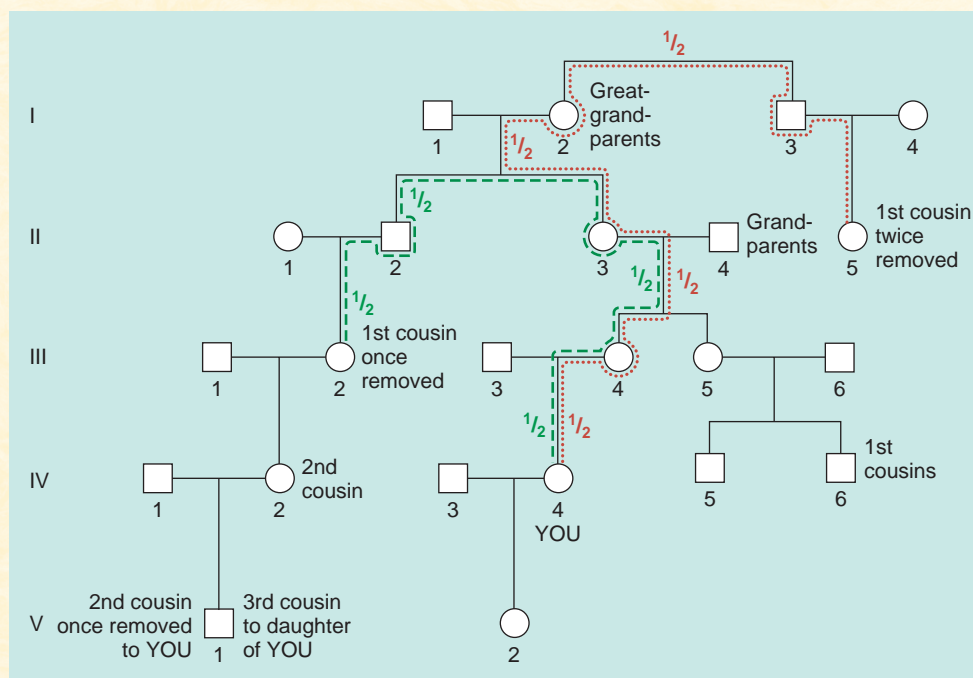
### Solving a Problem: Connecting Cousins

With more genetic tests becoming available as the human genome sequence is analyzed, more people are learning that relatives beyond their immediate families have certain gene variants that might affect their health. Because the genetic closeness of the relationship impacts the risk of developing certain conditions, it is helpful to calculate the percentage of the genome that two relatives share.

The pedigree in **figure 1** displays an extended family, with “YOU” as the starting point. Calculate the percent of the genome shared for your first cousins once and twice removed (that is, removed from you by one or two generations, respectively)—in the figure, in generations III and II, while YOU are in generation IV. A second, third, or fourth cousin, by contrast, is in the same generation on a pedigree as the individual in question; see, for example, individual V-1 in figure 1. **Table 1** summarizes the genetic relationships between cousins.

#### SOLUTION

The rules: Every step between parent and child, or sibling and sibling, has a value of  $1/2$ , because these types of pairs share



**Figure 1** Pedigrees help determine the percentage of the genome two relatives share.

approximately  $1/2$  of their genes, according to Mendel’s first law (chromosome segregation).

**Table 7.3**

#### Heritabilities for Some Human Traits

Trait	Heritability
Clubfoot	0.8
Height	0.8
Blood pressure	0.6
Body mass index	0.5
Verbal aptitude	0.7
Mathematical aptitude	0.3
Spelling aptitude	0.5
Total fingerprint ridge count	0.9
Intelligence	0.5–0.8
Total serum cholesterol	0.6

but certain variants much more common in one group due to long-term environmental differences. Populations in equatorial Africa, for example, have darker skin than sun-deprived Scandinavians.

Researchers use several statistical methods to estimate heritability. One way is to compare the actual proportion of pairs of people related in a certain manner who share a particular trait, to the expected proportion of pairs that would share it if it were inherited in a Mendelian fashion. The expected proportion is derived by knowing the blood relationships of the individuals and using a measurement called the **coefficient of relatedness**, which is the proportion of genes that two people related in a certain way share (**table 7.4**).

A parent and child share 50 percent of their genes, because of the mechanism of meiosis. Siblings share on average 50 percent of their genes, because they have a 50 percent chance of inheriting each allele for a gene from each parent. Genetic counselors use the designations of primary ( $1^\circ$ ), secondary ( $2^\circ$ ), and tertiary ( $3^\circ$ ) relatives when calculating risks (**table 7.4** and **figure 7.6**). For extended or complicated pedigrees, the value of  $1/2$  or 50 percent between siblings and between parent-child pairs can be used to trace and calculate the percentage of genes shared between people related in other ways. **Reading 7.1** discusses how to calculate percentages of the genome shared for first cousins separated by generations, described as “removed” by one or more generations.



Table 1

## Percent of Genome Shared by Cousins

Type of Cousin	Definition	Shared Genes
First	Share 2 grandparents	1/8
Second	Share great-grandparents but no grandparents	1/16
Third	Share great-great grandparents	1/32
Fourth	Share great-great-great grandparents	1/64
Once removed	One generation difference between relatives	1/16
Twice removed	Two generations difference between relatives	1/32

**First cousin once removed (in green):**

you to your mother	=1/2
your mother to her mother (your grandmother)	=1/2
your grandmother to her brother (your great uncle)	=1/2
your great uncle to his daughter (your first cousin)	=1/2
$1/2 \times 1/2 \times 1/2 \times 1/2 = 1/16$	

**First cousin twice removed (in red):**

you to your mother	=1/2
your mother to her mother (your grandmother)	=1/2
your grandmother to her mother (your great-grandmother)	=1/2
your great-grandmother to her brother	=1/2
your great-grandmother's brother to his daughter	=1/2
$1/2 \times 1/2 \times 1/2 \times 1/2 \times 1/2 = 1/32$	

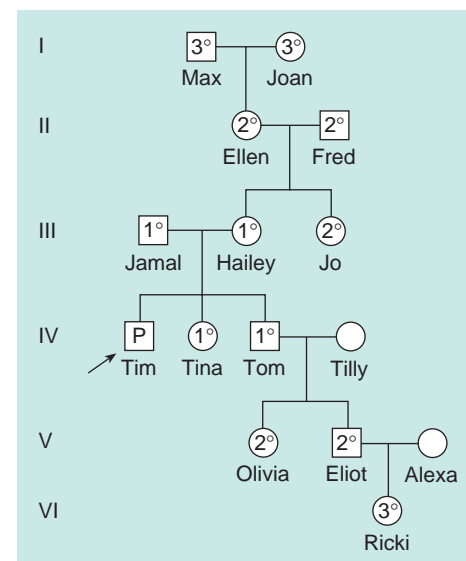
Table 7.4

## Coefficient of Relatedness for Pairs of Relatives

Relationship	Degree of Relationship	Percent Shared Genes (Coefficient of Relatedness)
Sibling to sibling	1°	50% (1/2)
Parent to child	1°	50% (1/2)
Uncle/aunt to niece/nephew	2°	25% (1/4)
Grandparent to grandchild	2°	25% (1/4)
First cousin to first cousin	3°	12 1/2% (1/8)

If the heritability of a trait is very high, then of a group of 100 sibling pairs, nearly 50 would be expected to have the same phenotype, because siblings share on average 50 percent of their genes. Height is a trait

for which heritability reflects the environmental influence of nutrition. Of 100 sibling pairs in a population, for example, 40 might be the same number of inches tall. Heritability for height among this group of



**Figure 7.6 Tracing relatives.** Tim has an inherited illness. A genetic counselor drew this pedigree to explain the approximate percentage of genes Tim shares with relatives. This information can be used to alert certain relatives to the risk by which they or their offspring might be affected.

("P" is the proband, or affected individual who initiated the study. See table 7.4 for definitions of 1°, 2°, and 3° relationships. Individuals with no relationship indicated are not blood relatives of the proband.)

sibling pairs is .40/.50, or 80 percent, which is the observed phenotypic variation divided by the expected phenotypic variation if environment had no influence.

Genetic variance for a polygenic trait is mostly due to the additive effects of recessive alleles of different genes. For some traits, a few dominant alleles can greatly influence the phenotype, but because they are rare, they do not contribute greatly to heritability. This is the case for heart disease caused by a faulty LDL receptor. Epistasis (interaction between alleles of different genes) can also influence heritability. To account for the fact that different genes affect a phenotype to differing degrees, geneticists calculate a "narrow" heritability that considers only additive recessive effects, and a "broad" heritability that also considers the effects of rare dominant alleles and epistasis. For LDL cholesterol level, for example, the narrow heritability is 0.36, but the broad heritability is 0.96, reflecting the fact that a rare dominant allele has a large impact. The ability to taste bitter substances is another trait that

is largely determined by one gene, on chromosome 7, but influenced by several other genes with less influence, but that add up.

Understanding multifactorial inheritance is important in agriculture. A breeder needs to know whether genetic or environmental variation mostly determines such traits as birth weight, milk yield, length of wool fiber, and egg hatchability. It is also valuable to know whether the genetic influences are additive or epistatic. The breeder can control the environment by adjusting the conditions under which animals are raised and crops grown, and the inherited trait variant input by setting up matings and crosses between particular individuals.

Studying multifactorial traits in humans is difficult, because information must be obtained from many families. Two special types of people, however, can help geneticists to tease apart the genetic and environmental components of multifactorial traits—adopted individuals and twins.

### Key Concepts

- 1. Empiric risk applies population incidence data to predict risk of recurrence for a multifactorial trait or disorder.
- 2. Heritability measures the genetic contribution to a multifactorial trait; it is specific to a particular population at a particular time.
- 3. A coefficient of relatedness, the proportion of genes that individuals related in a certain way are expected to share, is used to calculate heritability.

### Adopted Individuals

A person adopted by people who are not blood relatives shares environmental influences, but typically not many genes, with the adoptive family. Conversely, adopted individuals share genes, but not the exact environment, with their biological parents. Therefore, biologists assume that similarities between adopted people and adoptive parents reflect mostly environmental influences, whereas similarities between adoptees and their biological parents reflect mostly genetic influences. Information on both sets of parents can reveal how heredity and the environment contribute to a trait.

Many early adoption studies used a database of all adopted children in Denmark and their families from 1924 to 1947. One study examined correlations between causes of death among biological and adoptive parents and adopted children. If a biological parent died of infection before age 50, the adopted child was five times more likely to die of infection at a young age than a similar person in the general population. This may be because inherited variants in immune system genes increase susceptibility to certain infections. In support of this hypothesis, the risk that an adopted individual would die young from infection did not correlate with adoptive parents' death from infection before age 50. Although researchers concluded that length of life is mostly determined by heredity, they did find evidence of environmental influences. For example, if adoptive parents died before age 50 of cardiovascular disease, their adopted children were three times as likely to die of heart and blood vessel disease as a person in the general population. What environmental factor might explain this correlation?

### Twins

Studies that use twins to separate the genetic from the environmental contribution to a phenotype provide more meaningful information than studying adopted individuals. Twin studies have largely replaced adoption methods.

Using twins to study genetic influence on traits dates to 1924, when German dermatologist Hermann Siemens compared

school transcripts of identical versus fraternal twins. Noticing that grades and teachers' comments were much more alike for identical twins than for fraternal twins, he proposed that genes contribute to intelligence.

A trait that occurs more frequently in both members of identical (monozygotic or MZ) twin pairs than in both members of fraternal (dizygotic or DZ) twin pairs is at least partly controlled by heredity. Geneticists calculate the **concordance** of a trait as the percentage of pairs in which both twins express the trait among pairs of twins in whom at least one has the trait. Twins who differ in a trait are said to be discordant for it.

In one study, 142 MZ twin pairs and 142 DZ twin pairs took a "distorted tunes test," in which 26 familiar songs were played, each with at least one note altered. A person was considered "tune deaf" if he or she failed to detect the mistakes in three or more tunes. Concordance for "tune deafness" was 67 percent for MZ twins, but only 44 percent for DZ twins, indicating a considerable inherited component in the ability to accurately perceive musical pitch. **Table 7.5** compares twin types for a variety of hard-to-measure traits. (Figure 3.16 shows how DZ and MZ twins arise.)

Diseases caused by single genes that are 100 percent penetrant, whether dominant or recessive, are 100 percent concordant in MZ twins. If one twin has the disease, so does the other. However, among DZ twins, concordance generally is 50 percent for a dominant trait and 25 percent for a recessive trait. These are the Mendelian values that apply to any two siblings. For a

Table 7.5

Concordance Values for Some Traits in Twins

Trait	Concordance	
	MZ (identical) twins	DZ (fraternal) twins
Acne	14%	14%
Alzheimer disease	78%	39%
Anorexia nervosa	55%	7%
Autism	90%	4.5%
Bipolar disorder	33–80%	0–8%
Cleft lip with or without cleft palate	40%	3–6%
Hypertension	62%	48%
Schizophrenia	40–50%	10%

polygenic trait with little environmental input, concordance values for MZ twins are significantly greater than for DZ twins. A trait molded mostly by the environment exhibits similar concordance values for both types of twins.

Comparing twin types assumes that both types of twins share similar experiences. In fact, MZ twins are often closer emotionally than DZ twins. This discrepancy between the closeness of the two types of twins can lead to misleading results. A study from the 1940s, for example, concluded that tuberculosis is inherited because concordance among MZ twins was higher than among DZ twins. Actually, the infectious disease more readily passed between MZ twins because their parents kept them closer. However, the 1940s study wasn't totally off the mark. We do inherit susceptibilities to some infectious diseases. MZ twins would share such genes, whereas DZ twins would only be as likely as any sibling pairs to do so.

For some traits for which the abnormality may produce symptoms before birth, the type of MZ twin may be important. That is, MZ twins with the same amnion may share more environmental factors than MZ twins who have separate amnions (see figure 3.16). Schizophrenia is a condition that may begin subtly, before birth, and later become obvious when environmental factors come into play. Schizophrenia is discussed in chapter 8.

A more informative way to assess the genetic component of a multifactorial trait is to study MZ twins who were separated at birth, then raised in very different environments. Much of the work using this “twins reared apart” approach has taken place at the University of Minnesota. Here, since 1979, hundreds of sets of twins and triplets who were separated at birth have visited the laboratories of Thomas Bouchard. For a week or more, the twins and triplets are tested for physical and behavioral traits, including 24 different blood types, handedness, direction of hair growth, fingerprint pattern, height, weight, functioning of all organ systems, intelligence, allergies, and dental patterns. Researchers videotape facial expressions and body movements in different circumstances and probe participants’ fears, interests, and superstitions.

Twins and triplets separated at birth provide natural experiments for distinguishing

nature from nurture. Many of their common traits can be attributed to genetics, especially if their environments have been very different. By contrast, their differences tend to reflect differences in upbringing, since their genes are identical (MZ twins and triplets) or similar (DZ twins and triplets).

MZ twins and triplets separated at birth and reunited later are remarkably similar, even when they grow up in very different adoptive families (figure 7.7). Idiosyncrasies are particularly striking. For example, one pair of twins who met for the first time when they were in their thirties responded identically to questions; each paused for 30 seconds, rotated a gold necklace she was wearing three times, and then answered the question. Coincidence, or genetics?

The “twins reared apart” approach is not an ideal way to separate nature from nurture. MZ twins and other multiples share an environment in the uterus and possibly in early infancy that may affect later development. Siblings, whether adoptive or biological, do not always share identical home environments. Differences in sex, general health,

school and peer experiences, temperament, and personality affect each individual’s perception of such environmental influences as parental affection and discipline.

Adoption studies, likewise, are not perfectly controlled experiments. In the past, adoption agencies tended to search for adoptive families with ethnic, socioeconomic, or religious backgrounds similar to those of the biological parents. Thus, even when different families adopted and raised separated twins, their environments were not as different as they might have been for two unrelated adoptees.

## Association Studies

Empiric risk, heritability, and adoptee and twin studies are traditional ways of estimating the degree to which genes contribute to the variability of a trait or illness. The availability of the human genome sequence is enabling researchers to build on these older techniques to identify specific genes that contribute to multifactorial traits and disorders. Whereas analysis of single-gene traits often followed linkage patterns in



Separated at birth, the Mallifert twins meet accidentally.

### Figure 7.7

Originally published in the 4 May 1981 issue of *The New Yorker* Magazine, p. 43. © Tee and Charles Addams Foundation. Reprinted by permission.



families, as discussed in chapter 5, discovering genome regions that “mark” polygenic diseases or traits entails population-level studies. Many such investigations use SNPs. (SNPs are useful to describe single-gene traits, too.)

Recall from chapter 1 that a SNP (pronounced “snip”), or single nucleotide polymorphism, is a specific site within a genome where the DNA base varies in at least 1 percent of a population. **Figure 7.8** shows a portion of a gene whose protein product enables a person to taste a very bitter substance. Three polymorphic sites identify two haplotypes that form two alleles—the corresponding phenotypes are either “taster” or “nontaster” (see figure 5.17). The trait is multifactorial because the ability to taste bitter substances would not be noticed unless one ate such foods.

Some SNPs are used as indirect markers of chromosomal areas where genes of

interest may be found. That is, if a particular SNP always occurs in individuals with a specific trait, then it may do so because it lies nearby on the same copy of the same chromosome—the SNP and disease-causing gene are linked. To make such “associations,” many SNPs are considered—but not too many.

In the human genome, a SNP occurs about every 1,200 bases, which adds up to about 10 million SNPs. Rather than tracking them all to identify associations with traits, disorders, or susceptibilities, researchers use the fact that SNPs near each other on the same chromosome tend to be inherited together in blocks of sequence. This traveling together is linkage disequilibrium, or LD, introduced in chapter 5. The 10 million SNPs in the human genome form about 500,000 haplotypes. A shortcut in gene hunting is to identify one SNP per haplotype, termed a tag SNP.

Thanks to tag SNPs, researchers need not sequence all 3.2 billion bases, nor even all 10 million SNPs. It is a little like recognizing many sports teams who have traveled to an event by identifying the captain of each team.

SNPs are used in **association studies**, in which researchers compare SNP patterns between a group of individuals who have a particular disorder and a group who do not. An association study may use a case-control design, in which each individual in one group is matched to an individual in the other group who shares as many characteristics as possible, such as age, sex, activity level, and environmental exposures. SNP differences are then correlated to the presence or absence of the disorder. For example, if 500 individuals with hypertension (high blood pressure) have particular DNA bases at six sites in the genome, and 500 matched individuals who do not have hypertension have different bases at only these six sites, then these genome regions may include genes whose protein products control blood pressure. When many SNPs are considered, many susceptibility genes can be tracked.

An association study is more meaningful if it borrows from the older technique of looking at family members. In the “affected sibling pair” strategy, researchers scan genomes for SNPs that most siblings who have the same condition share, but that siblings who do not both have the condition do not often share. Such genome regions may harbor genes that contribute to the condition. The logic is that because siblings share 50 percent of their genes, a trait or condition that many siblings share is likely to be inherited. One affected sibling pair analysis examined 500 pairs of siblings who both have hypertension, and 500 pairs of siblings who do not. Genome regions for which all (or most) of the 500 affected siblings have the same SNPs, but few of the other group do, suggest possible sites of genes that contribute to the trait.

A related approach examines case-parent trios and identifies SNPs that a child who has a certain disorder shares with one parent but not the other. In one study, 440 SNPs were tracked in threesomes in which a child and one parent suffer from schizophrenia, narrowing the search for causative genes.

#### PTC gene, non-taster allele

```

1      atgttgactc taactcgcat cgcactgtg tcctatgaag tcaggagtac atttctgttc
61..   atttcagtc tggagtttgc agtggggttt ctgaccaatg ccttcgtttt cttggtgaat
121..  ttttgggatg tagtgaagag gcagcactg agcaacagtg atttgtgtct gctgtgtctc
...

781    tgtgtgcct tcactctctgt gccctactg attctgtggc gcgacaaaat aggggtgatg
841    gtttgtgttg ggataatggc agcttgtccc tctgggcatg cagccatcct gatctcaggc
901    aatgccaagt tgaggagagc tgtgatgacc attctgtctc gggctcagag cagcctgaag
961    gtaagagccg accacaaggc agattcccg acactgtgct ga

```

#### PTC gene, taster allele

```

1      atgttgactc taactcgcat cgcactgtg tcctatgaag tcaggagtac atttctgttc
61..   atttcagtc tggagtttgc agtggggttt ctgaccaatg ccttcgtttt cttggtgaat
121..  ttttgggatg tagtgaagag gcagcactg agcaacagtg atttgtgtct gctgtgtctc
...

781    tgtgtgcct tcactctctgt gccctactg attctgtggc gcgacaaaat aggggtgatg
841    gtttgtgttg ggataatggc agcttgtccc tctgggcatg cagccatcct gatctcaggc
901    aatgccaagt tgaggagagc tgtgatgacc attctgtctc gggctcagag cagcctgaag
961    gtaagagccg accacaaggc agattcccg acactgtgct ga

```

**Figure 7.8 SNPs are sites of variability in genomes.** These two sets of DNA base sequences represent a gene that controls the ability to taste phenylthiocarbamide (PTC). About 70 percent of individuals taste an extremely bitter substance when they lick a paper containing PTC; the other 30 percent taste nothing at all. Sequencing the PTC gene revealed differences at three sites. In the illustration, the numbers on the left are guidelines to position within the gene—the entire gene is 1,003 bases long. The bases are displayed in groups of ten for ease of counting. In a nontaster, positions 145, 785, and 886 are G, T, and A, respectively. In a taster, these three DNA bases are instead C, C, and G. The changes substitute three different amino acids in the encoded protein, which is sufficient to alter the phenotype.

It takes a great deal of research to test whether SNP patterns are actually meaningful. For example, if a SNP pattern in a population is associated with breast cancer, then the next step is to see if these tumors are different, at a cell and tissue level, from other cases of breast cancer. Software can compare SNP and histological data to see if the SNP pattern accurately reflects a physically distinct subtype of the disease. If it does, a SNP scan might replace or augment microscopic analysis of the tumor.

SNP association studies have many applications. They identify DNA sequence differences among individuals much more quickly than sequencing entire genomes. It is a little like quickly noting distinctive items of clothing on two individuals instead of listing everything they are wearing. Identifying the SNPs that travel with genes of interest will enable researchers to search human genome data to identify nearby genes whose protein products could be absent or altered in a way that explains symptoms. These become “candidates” in the search for disease-causing genes. All of this is necessary because even though the human genome has been sequenced, we do not yet know what all of the genes do.

A limitation of association studies is that they establish correlations, not causation. It is rare to find a DNA sequence that contributes to a polygenic trait exclusively in affected individuals. Return to the example of the SNP pattern associated with hypertension. If the study were to be extended to include 10,000 people in each group, rather than just 500, the association could fall apart. This has in fact happened when many association studies have been extended to include more people. This would mean that the genes being traced are not the only ones that contribute to the phenotype of hypertension.

The more complex a SNP association study, the more individuals are required to achieve statistical significance. Consider an investigation that examines 20 genes, each with 4 SNPs, that contribute to development of a particular polygenic disease. A screen would look for 160 data points per individual ( $20 \text{ genes} \times 4 \text{ SNPs/gene} \times 2 \text{ copies of each gene} = 160 \text{ data points}$ ). With thousands of possible combinations (genotypes), it's clear that *many* thousands of individuals would have to be examined to note any correlations between the SNP pattern and disease.

Association studies are also limited by some of the complications of Mendel's laws discussed in chapter 5, as follows:

- Genetic heterogeneity confounds associations between SNPs and phenotypes if those phenotypes are caused by different genes.
- For late-onset disorders, young people might be classified as wild type (healthy) when they have actually inherited a genotype that has not yet affected their health.
- In cases of incomplete penetrance, individuals would be classified as wild type who are not, based on their healthy phenotype.
- If a trait is a phenocopy, its cause is environmental and not genetic, so any association with a SNP pattern is meaningless.

It is interesting to see how old and new studies can come together to describe the origins of a multifactorial trait. This is the case for stuttering. Various studies have found concordance for MZ twins to range from 20 to 83 percent, and for DZ twins to range from 4 to 9 percent, suggesting a large inherited component. The risk of a first-degree relative of a person who stutters also stuttering is 15 percent based on empiric evidence, compared to the lifetime risk of stuttering in the general population of 5 percent, although part of that increase could be due to imitative behavior. More recently, a whole genome scan encompassing 10,000 SNPs was performed on 100 families who have at least two members

who stutter. The study identified genes on three chromosomes.

Another example of recent technology extending what we can learn from older approaches is to identify differences in gene expression in MZ twins who are discordant for a trait. Rather than providing information on inherited disease, this strategy describes diseases that are not inherited, but nevertheless affect the ways that genes are used. Consider rheumatoid arthritis, a severe form of arthritis that is autoimmune and not inherited. A study identified genes that were greatly overexpressed in a group of people who have the arthritis, but whose identical twins do not. Three genes were implicated. Increased expression of one gene, which produces an enzyme that degrades bone, was already known to be part of the disease, but the other two dysregulated genes were not. So even though the study didn't reveal how the arthritis starts, or how it can affect one twin but not the other, researchers now have two new drug targets.

The U.S. government is coordinating efforts among researchers who are conducting “genome-wide association studies.” These investigations, which include SNP maps as well as maps based on repeated DNA sequences, are seeking patterns of genetic variation that correlate to a host of multifactorial traits and disorders, including susceptibility to them. In this way, more common health problems can be dissected at the molecular level, offering information that can be used to develop new prevention strategies as well as treatments.

**Table 7.6** reviews terms used in the study of multifactorial traits.

Table 7.6

Terms Used in Evaluating Multifactorial Traits

<b>Association study</b>	Detecting correlation between SNP (or other marker) patterns and increased risk of developing a particular medical condition.
<b>Coefficient of relatedness</b>	The proportion of genes shared by two people related in a particular way. Used to calculate heritability.
<b>Concordance</b>	The percentage of twin pairs in which both twins express a trait.
<b>Empiric risk</b>	The risk of recurrence of a trait or illness based on known incidence in a particular population.
<b>Heritability</b>	The percentage of phenotypic variation for a trait that is attributable to genetic differences. It equals the ratio of the observed phenotypic variation to the expected phenotypic variation for a population of individuals.

## Key Concepts

1. Researchers compare traits in adopted individuals to those in their adoptive and biological parents to assess the genetic contribution to a trait.
2. Concordance is the percentage of twin pairs in which both express a trait. For a trait largely determined by genes, concordance is higher for MZ than DZ twins.
3. Association studies seek correlations between SNP patterns and phenotypes in large groups of individuals.

## 7.3 Two Multifactorial Traits

Multifactorial traits include such common conditions as heart and blood vessel (cardiovascular) disease and body weight. Chapter 8 examines harder-to-define traits, including intelligence and aspects of personality, mood, and behavior.

### Heart Health

Cardiovascular diseases tend to be multifactorial because many types of cells and processes must interact for the heart and vessels to effectively and continuously circulate blood. It isn't surprising that many genes take part in the system's maintenance. Effects of the environment are great, too. Even single-gene cardiovascular diseases are affected by outside influences. For example, intake of vitamin K, necessary for blood to clot, influences the severity of single-gene clotting disorders.

Genes control cardiovascular functioning in several ways: transporting lipids; blood clotting; blood pressure; and how well cellular adhesion molecules enable white blood cells to stick to the walls of blood vessels (see figure 2.20). Lipids can only move in the circulation when bound to proteins to form large molecules called lipoproteins. Several genes encode the protein parts of lipoproteins, which are called apolipoproteins. Some types of lipoproteins carry lipids in the blood to tissues, where they are utilized, and other types of

lipoproteins take lipids to the liver, where they are dismantled into biochemicals that the body can excrete more easily. One allele of a gene that encodes apolipoprotein E, called E4, increases the risk of a heart attack threefold in people who smoke. This is clear evidence that genes and environmental factors can interact in ways that cause illness.

Maintaining a healthy cardiovascular system requires a lipid balance: Cells require sufficient lipid levels inside but cannot allow accumulation on the outside. Several dozen genes control lipid levels in the blood and tissues by specifying enzymes that process lipids, proteins that transport them, or receptor proteins that admit lipids into cells.

An enzyme, lipoprotein lipase, is important in lipid metabolism. It lines the walls of the smallest blood vessels, where it breaks down fat packets released from the small intestine and liver. Lipoprotein lipase is activated by high-density lipoproteins (HDLs), and it breaks down low-density lipoproteins (LDLs). High HDL levels and low LDL levels are associated with a healthy cardiovascular system. In inborn errors of metabolism called type 1 hyperlipoproteinemias, too little lipoprotein lipase causes triglycerides (a type of fat) to reach dangerously high levels in the blood. Lipoprotein lipase also regulates fat cell size; fat cells contribute to obesity by enlarging, rather than dividing.

The fluidity of the blood is also critical to health. Overly active clotting factors or extra sticky white blood cells can induce formation of clots that block blood flow, usually in blood vessels in the heart or in the legs.

At least 50 genes regulate blood pressure. One gene encodes angiotensinogen, a protein that is elevated in the blood of people with hypertension. This protein controls blood vessel tone and fluid balance. Certain alleles are much more common among people with hypertension than chance would explain. Even though environmental factors, such as emotional stress, can raise blood pressure, knowing who is genetically susceptible can alert doctors to monitor high-risk individuals.

Genetic test panels detect multiple alleles in dozens of genes that cause or contribute to cardiovascular disease. DNA microarrays can monitor gene expression, assessing many contributing factors. For example, one gene expression microarray test can indicate which cholesterol-lowering drugs are most likely to be effective and without side effects. The premise behind the value of such information is that people have composite genetic risks based on the small contributions of several genes—the essence of polygenic inheritance. Computer analysis of multigene tests accounts for environmental factors (table 7.7). Some risk factors are controllable with lifestyle changes, such as exercising, not smoking, and maintaining a healthy weight.

Table 7.7

Risk Factors for Cardiovascular Disease

Uncontrollable	Controllable
Age	Fatty diet
Male sex	Hypertension
Genes	Smoking
Lipid metabolism	High serum cholesterol
Apolipoproteins	Low serum HDL
Lipoprotein lipase	High serum LDL
Blood clotting	Stress
Fibrinogen	Insufficient exercise
Clotting factors	Obesity
Homocysteine metabolism	Diabetes
Leukocyte adhesion	



# Weight

Body weight reflects energy balance—the rate of food taken in versus the rate at which the body uses it for fuel. Excess food means, ultimately, excess weight. About 30 percent of all adults in the United States are obese,

and another 35 percent are overweight. Being overweight or obese raises the risk of developing hypertension, diabetes, stroke, gallstones, sleep apnea, and some cancers.

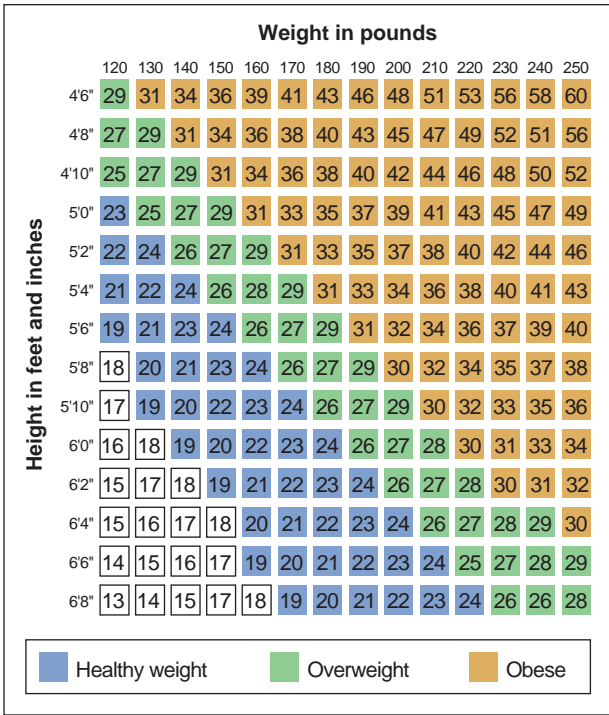
Scientific studies of body weight use a measurement called body mass index (BMI), which is weight in proportion to height

(figure 7.9). BMI makes sense—a person who weighs 170 pounds and is 6 feet tall is slim, whereas a person of the same weight who is 5 feet tall is obese. The tall person’s BMI is 23; the short person’s is 33.5.

Heritability for BMI is 0.55, which leaves room for environmental influences on our appetites and sizes. Yet the genetic picture is complex. Genomewide screens for SNPs associated with BMI point to at least 50 different regions likely to harbor genes that affect how much we eat, how we use calories, and how fat is distributed in the body. Weight is controlled by biochemical pathways and hormonal interactions that may reveal points for drug intervention (table 7.8).

## Leptin and Associated Proteins

Obesity research first embraced genetics in 1994, when Jeffrey Friedman at Rockefeller University discovered a gene that encodes the protein hormone leptin in mice and in humans. Normally, eating stimulates fat cells (adipocytes) to secrete leptin. It travels in the bloodstream to a region of the brain’s hypothalamus, where it binds to receptors on nerve cells (neurons). The binding signals the neurons to release another type of hormone that binds yet other types of receptors, which ultimately function as an appetite “brake,” while speeding breakdown of food already eaten. When a person hasn’t eaten in several hours, leptin levels ebb, which triggers the release of an



Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion

**Figure 7.9 Body mass index (BMI).** BMI equals weight/height<sup>2</sup>, with weight measured in kilograms and height measured in meters. This chart provides a shortcut—the calculations have been done and converted to the English system of measurement. Squares that are not filled in indicate underweight.

**Table 7.8**

Some Sites of Genetic Control of Body Weight			
Protein	Function	OMIM	Effect on Appetite
Leptin	Stimulates cells in hypothalamus to decrease appetite and metabolize nutrients.	164160	↓
Leptin transporter	Enables leptin to cross from bloodstream into brain.	601694	↓
Leptin receptor	Binds leptin on hypothalamus cell surfaces, triggering hormone’s effects.	601007	↓
Neuropeptide Y	Produced in hypothalamus when leptin levels are low and the individual loses weight.	162640	↑
Melanocortin-4 receptor	Activated when leptin levels are high and the individual gains weight.	155541	↓
Ghrelin	Signals hungers from stomach to brain in short term, stimulating neuropeptide Y.	605353	↑
PYY	Signals satiety from stomach to brain.	660781	↓
Stearoyl-CoA desaturase-1	Controls whether body stores or uses fat.	604031	↑



a.



b.

**Figure 7.10 The environment influences gene expression.** Comparison of average body weights among the Arizona population of Pima Indians (a) and the Mexican population (b) reveals the effects of the environment.

appetite “accelerator.” Table 7.8 lists the details of some proteins that affect eating behavior.

The discovery of genes and proteins that affect appetite led to great interest in targeting them with drugs to either lose or gain weight. When Friedman gave mice extra leptin, they ate less and lost weight. Headlines soon proclaimed the new magic weight loss elixir, a biotech company paid \$20 million for rights to the hormone, and clinical trials ensued. The idea was to give obese people leptin, assuming that they had a deficiency, to trick them into feeling full. Only about 15 percent of the people lost weight, but the other 85 percent didn’t actually lack leptin. Instead, most of them had leptin resistance, which is a diminished ability to recognize the hormone due to defective leptin receptors. Giving these people leptin had no effect on their appetites.

Despite disappointing clinical trials with leptin, the discovery fueled further research, and some people have benefited. A few severely obese children with true leptin deficiency have attained normal weights with daily leptin injections. One 9-year-old weighed more than 200 pounds and would eat in one meal what an adult would consume in half a day. Leptin injections dropped her weight to normal within four years.

The stomach is another source of obesity-related proteins. Ghrelin is a peptide (small protein) hormone produced in the stomach that responds to hunger, signaling the hypothalamus to produce more of the appetite accelerator. A different peptide hormone opposes ghrelin, signaling satiety to the brain. While leptin acts in the long term to maintain weight, the stomach’s appetite control hormones function in the short term. All of these hormonal signals are integrated to finely control appetite in a way that maintains weight.

### Environmental Influences on Obesity

Many studies on adopted individuals and twins suggest that obesity has a heritability of 75 percent. Because the heritability for BMI is lower than this, the discrepancy suggests that genes play a larger role in those who tend to gain weight easily. This becomes obvious when populations that have a genetic tendency to obesity experience a drastic and sudden change in diet for the worse.

On the tiny island of Nauru, in Western Samoa, the residents’ lifestyles changed greatly when they found a market for the tons of bird droppings on their island as commercial fertilizer. The influx of money translated into inactivity and a high-calorie, high-fat diet, replacing an agricultural

lifestyle and a diet of fish and vegetables. Within just a generation, two-thirds of the population had become obese, and a third suffered from diabetes.

The Pima Indians offer another example of environmental effects on body weight (**figure 7.10**). These people separated into two populations during the Middle Ages, one group settling in the Sierra Madre mountains of Mexico, the other in southern Arizona. By the 1970s, the Arizona Indians no longer farmed nor ate a low-calorie, low-fat diet, but instead consumed 40 percent of their calories from fat. With this extreme change in lifestyle, they developed the highest prevalence of obesity of any population on earth. Half of the Arizona group had diabetes by age 35, weighing, on average, 57 pounds (26 kilograms) more than their southern relatives, who still eat a low-fat diet and are very active.

The Pima Indians demonstrate that future obesity is not sealed in the genes at conception, but instead is much more likely to occur if the environment provides too many calories and too much fat. They illustrate what geneticist James Neel termed the “thrifty gene hypothesis” in 1962. He suggested that long ago, the hunter-gatherers who survived famine had genes that enabled them to efficiently conserve fat. Today, with food plentiful, the genetic tendency to retain fat is no longer healthful,

but harmful. Unfortunately, for many of us, our genomes hold an energy-conserving legacy that works too well—it is much easier to gain weight than to lose it, for sound evolutionary reasons.

Another environmental influence on weight is the types of bacteria in our bodies. Recall from chapter 1 that bacterial cells in our bodies actually outnumber our own cells. The actions of certain types of bacteria affect the number of calories that we extract from particular foods. Researchers demonstrated this by controlling the diets of a group of obese individuals and monitoring the bacterial species in their feces. The investigators identified nine

species of bacteria that enable a human body to extract maximal calories from food. Harboring these bacteria and being overweight is termed “infectobesity.”

Interactions and contributions of genes and the environment provide some of the greatest challenges in studying human genetics. Why does one smoker develop lung cancer, but another does not? Why can one person consistently overeat and never gain weight, while another gains easily? Because we exist in an environment, no gene functions in a vacuum. Subtle interactions of nature and nurture profoundly affect our lives and make us all—even identical twins—unique individuals.

## Key Concepts

1. Genes that affect lipid metabolism, blood clotting, leukocyte adhesion, and blood pressure influence cardiovascular health.
2. Genes that encode leptin, the leptin receptor, and proteins that transmit or counter leptin’s signals affect body weight.
3. Studies on adopted individuals and twins indicate a heritability of 75 percent for obesity.
4. Populations that suddenly become sedentary and switch to a fatty diet reflect environmental influences on body weight.

## Summary

### 7.1 Genes and the Environment Mold Most Traits

1. **Multifactorial traits** reflect the environment and genes. A **polygenic trait** is determined by more than one gene and varies continuously in expression. The frequency distribution of phenotypes for a polygenic trait forms a bell curve.

### 7.2 Investigating Multifactorial Traits

2. **Empiric risk** measures the likelihood that a multifactorial trait will recur based on its prevalence in a population. The risk rises as genetic closeness to an affected individual increases, as the severity of the phenotype increases, and as the number of affected relatives rises.

3. **Heritability** estimates the proportion of variation in a multifactorial trait that is attributable to genetic variation. It describes a trait in a particular population at a particular time. Heritability compares the actual incidence of a shared trait among people related in a certain way to the expected incidence. Rare dominant alleles can contribute to heritability.
4. Characteristics shared by adopted people and their biological parents are mostly inherited, whereas similarities between adopted people and their adoptive parents reflect environmental influences.
5. **Concordance** measures the frequency of expression of a trait in both members of MZ or DZ twin pairs. The more influence genes exert over a trait, the higher the

differences in concordance between MZ and DZ twins.

6. **Association studies** correlate SNP patterns to increased risk of developing a disorder.

### 7.3 Two Multifactorial Traits

7. Genes that control lipid metabolism and blood clotting, blood pressure, and cell adhesion contribute to cardiovascular health.
8. Leptin and associated proteins affect appetite and therefore weight. Fat cells secrete leptin in response to eating, and the protein acts in the hypothalamus to decrease appetite. Populations that switch to a fatty, high-calorie diet and a less-active lifestyle reveal the effects of the environment on weight.

## Review Questions

1. Explain how Mendel’s laws apply to multifactorial traits.
2. Consider the traits of eye color and body weight. Which is more likely to be inherited as a single-gene trait, and which is multifactorial? Cite reasons for your answer.
3. What is the difference between a Mendelian multifactorial trait and a polygenic multifactorial trait?
4. Which has a greater heritability—eye color or height? State a reason for your answer.
5. How can skin color have a different heritability at different times of the year?
6. Explain how the twins in figure 7.4 have such different skin colors.
7. In a large, diverse population, why are medium brown skin colors more common than very white or very black skin?
8. Using the information in figure 7.6, what percentage of genes does Tim share with
  - a. Joan?
  - b. Hailey?
  - c. Eliot?
  - d. Ricki?
9. Describe the type of information in a(n)
  - a. empiric calculation.
  - b. twin study.



- c. adoption study.
- d. association study.

10. Why does SNP mapping require extensive data?

- 11. Name three types of proteins that affect cardiovascular functioning and three that affect body weight.
- 12. How can older techniques to study multifactorial traits, such as twin and

adoption studies, be combined with newer techniques?

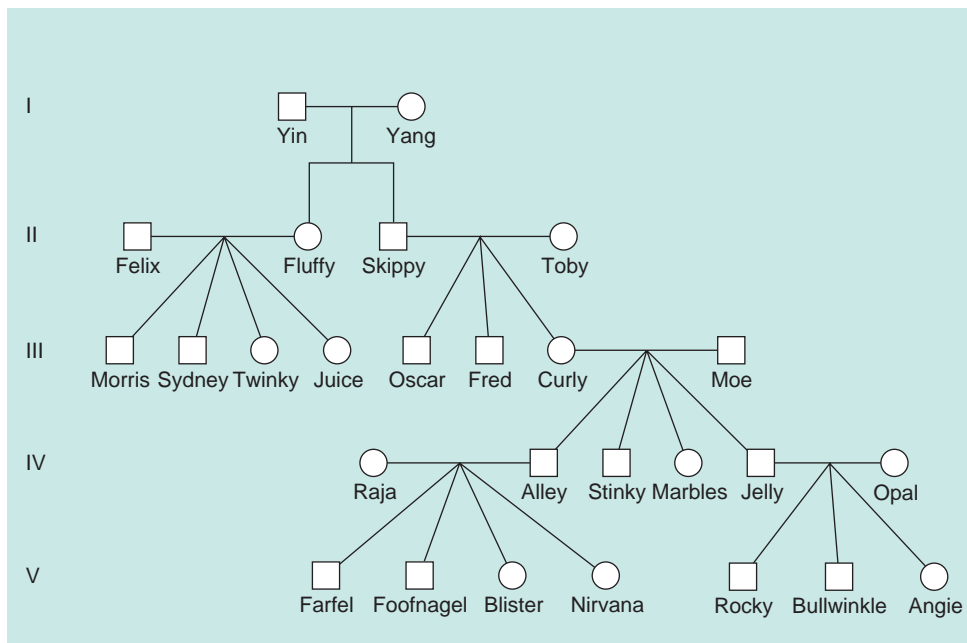
## Applied Questions

1. Rebecca breeds Maine coon cats. The partial pedigree to the right describes how her current cats are related—the umbrellalike lines indicate littermates, which are the equivalent of fraternal (DZ) twins in humans.

Cat lover Sam wishes to purchase a pair of Rebecca's cats to breed, but wants them to share as few genes as possible to minimize the risk that their kittens will inherit certain multifactorial disorders. Sam is quite taken with Farfel, but can't decide among Marbles, Juice, or Angie for Farfel's mate.

Calculate the percentage of genes that Farfel shares with each of these female relatives. With which partner would the likelihood of healthy kittens be greatest?

- 2. Do you think that tests for AAT deficiency (inherited emphysema) should be routinely given to individuals whose jobs expose their respiratory systems to irritants? Under what circumstances might this be helpful, and when could it be harmful?
- 3. Cite an example from chapter 5 of a single-gene trait or condition that is affected by an environmental influence.
- 4. Attention deficit hyperactivity disorder (ADHD) affects 5 percent of children and adolescents and 3 percent of adults. Individuals with ADHD have difficulty learning in a classroom situation where they must remain still and controlled. Heritability ranges from .6 to .9 in different populations. An adopted person is more likely to develop ADHD if a biological parent has the condition. An affected sibling pair association study using 270 pairs from the United States identified areas of chromosomes 16 and 17 that might harbor susceptibility genes. A study of 164 sib pairs in the Netherlands, however, pointed to sites on chromosomes 7 and 15.
  - a. Explain how the data indicate that ADHD is either more likely caused by inherited factors or environmental factors.



Maine coon cats

- b. Why might the results differ for different populations?
- c. What should the next step be in understanding the biological basis of ADHD?
- d. Drug treatment is widely used for ADHD. What would be an advantage of knowing which genes predispose a person to the condition?
- e. Suggest a possible danger in developing a genetic test for ADHD.
- 5. Would you take a drug that was prescribed to you based on your race? Cite a reason for your answer.
- 6. The incidence of obesity in the United States has doubled over the past two decades. Is this due more to genetic or environmental factors? Cite a reason for your answer.
- 7. One way to calculate heritability is to double the difference between the concordance values for MZ versus DZ twins. For multiple sclerosis, concordance for MZ twins is 30 percent, and for DZ twins, 3 percent. What is the heritability? What does the heritability suggest about the relative contributions of genes and the environment in causing MS?
- 8. Devise a SNP association study to assess whether restless legs syndrome is inherited, and if it is, where susceptibility or causative genes may be located.
- 9. How might the phenomenon of "infectobesity" affect the likelihood that twins are concordant for obesity compared to obesity among siblings who are not twins?
- 10. In chickens, high body weight is a multifactorial trait. Heritability accounts for several genes that contribute a small effect additively, as well as a few genes that exert a great effect. Is this an example of narrow or broad heritability?

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study**, chapter 7 and **Web Activities** to find the website links needed to complete the following activities.

11. Locate a website that deals with breeding show animals, farm animals, or crops to produce specific traits, such as litter size, degree of meat marbling, milk yield, or fruit ripening rate. Identify three traits with heritabilities that indicate a greater contribution from genes than from the environment.
  12. Visit the Centers for Disease Control and Prevention (CDC) website. From the leading causes of death, list three that have high heritabilities, and three that do not. Base your decisions on common sense or data, and explain your selections.
  13. Use OMIM to look up any of the following genes that affect cardiovascular health and explain what the genes do: apolipoprotein E; LDL receptor; apolipoprotein A; angiotensinogen; beta-2 adrenergic receptor; toll-like receptor 4; C-reactive protein.
- ### Case Studies and Research Results
14. Concordance for the eating disorder anorexia nervosa for MZ twins is 55 percent, and for DZ twins, 7 percent. Ashley and Maggie are DZ twins. Maggie has anorexia nervosa. Should Ashley worry about an inherited tendency to develop the condition? Explain your answer.
  15. Lydia and Reggie grew up poor in New York City in the 1960s. Both went for free to the City University of New York, then to medical school in Boston, where they met. Today, each has a thriving medical practice, and they are the parents of 18-year-old Jamal and 20-year-old Tanya. Jamal, taking a genetics class, wonders why he and Tanya do not resemble each other, or their parents, for some traits. The family is African American. Lydia and Reggie are short, 5'2" and 5'7" respectively, and each has medium brown eyes and skin, and dark brown hair. Tanya and Jamal are 5'8" and 6'1", respectively, and were often in the highest height percentiles since they were toddlers. Jamal has very dark skin, darker than his parents' skin, while Tanya's skin is noticeably lighter than that of either parent. Tanya's eyes are so dark that they appear nearly black.
    - a. Give two explanations for why Tanya's eyes appear darker than those of her parents or brother.
    - b. How can Jamal's skin be darker than that of his parents, and Tanya's be lighter?
  - c. Which of the four traits considered—height, and eye, skin, and hair color—is most influenced by environmental factors?
  - d. What is the evidence that Jamal and Tanya's height is due to environmental and genetic factors?
  - e. Which of the four traits has the highest heritability?
  16. A study looked at SNPs throughout the genome for 187 people with premature hair graying and 186 without this trait. Those with the trait shared several SNPs on chromosome 9. What type of study is this?
  17. "Elite controllers" are people with HIV infection whose immune systems naturally keep levels of the virus extremely low. Researchers are conducting genome-wide SNP analyses of these people. Explain how the results of this study might be used to help people who more easily develop AIDS.
  18. An affected sibling pair study identified areas of chromosomes 1, 14, and 20 that are likely to harbor genes that predispose individuals toward or cause schizophrenia. Explain how such an investigation is conducted.

## A Second Look

1. What evidence indicates that isolated cleft lip/palate involves quantitative trait loci?
2. The incidence of cleft lip with or without cleft palate (CL/CP) varies in different populations as follows:

Population	Incidence (per 1,000 births)
Africans	0.3
Europeans	1.0
European Americans	1.0
Indians	1.5
Asians	2.0
Native Americans	3.6

3. Would a black man and white woman, or two Asians, have a higher risk of having a child with CL/CP?
3. Consult Table 7.5 and cite two conditions that have a greater inherited component, according to concordance values, than isolated cleft lip/cleft palate.
4. Researchers have identified a gene, *IRF6*, that causes isolated cleft lip/cleft palate in some families. An ongoing study is investigating 150 SNPs located among more than 140,000 DNA bases surrounding this gene. Explain how haplotypes based on these SNPs might be used to predict risk for the condition in the general population.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

Complex traits among the Hutterites  
Vitiligo



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.





# Genetics of Behavior

## CHAPTER CONTENTS

- 8.1 Genes Contribute to Most Behavioral Traits
- 8.2 Eating Disorders
- 8.3 Sleep
  - Narcolepsy
  - Familial Advanced Sleep Phase Syndrome
- 8.4 Intelligence
- 8.5 Drug Addiction
- 8.6 Mood Disorders
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## CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome (CFS) usually begins with a flu-like illness, lasts at least six months, and causes disabling fatigue. Until recently, many people did not believe CFS was real. Genetics research may have finally proven them wrong.

Laura Hillenbrand, author of the bestseller *Seabiscuit*, has written about CFS. Ill since 1987, Laura, has been bedbound for months on end, too exhausted to do anything. The disease forced her to drop out of college, and she lost a great deal of weight. Doctors blamed infection, and sent her to a psychiatrist, who ruled out mental illness. Until she finally found a physician who knew that CFS was real, Hillenbrand's doctors told her the disabling symptoms were "all in your head." They weren't.

Clues to the cause of CFS lay in the observation that many people report a severe physical illness or emotional trauma before the fatigue began. Also, people with CFS make too little of the stress hormone cortisol, and too much of the nervous system chemical serotonin, which induces sleep and calms mood. Could an abnormal and persistent response to a trauma—physical or emotional—cause CFS? Secretions from the brain's hypothalamus and pituitary gland, and the adrenal glands, control responses to trauma. It was a logical place to look for CFS genes and their variants.

In 2006, a study indeed found three genes that differ in people with CFS. One gene encodes the receptor that binds stress hormones and the other two affect the availability of serotonin. A physical explanation for CFS may lead to treatment.



Chronic fatigue syndrome is not "all in one's head." It is likely due to an inherited extreme response to stress.

Behavioral traits include abilities, feelings, moods, personality, intelligence, and how a person communicates, copes with rage, and handles stress. Disorders with behavioral symptoms are wide-ranging and include phobias, anxiety, dementia, psychosis, addiction, and mood alteration.

Many aspects of our behavior occur in response to environmental factors, but *how* we respond may have genetic underpinnings. An added layer of complexity in understanding how behavioral traits and disorders arise is that people often pass judgment on what is considered abnormal behavior, as many of the half million people who suffer from chronic fatigue syndrome have discovered. This chapter explores how researchers are disentangling the genetic and environmental threads that contribute to several familiar behaviors and disorders.

## 8.1 Genes Contribute to Most Behavioral Traits

Very few medical conditions with behavioral components can be traced to a single gene. Most behavioral disorders fit the classic multifactorial disease profile: They affect more than 1 in 1,000 individuals and are caused by several genes and the environment.

Empiric risk estimates and adoptee and twin studies, discussed in chapter 7, indicate that nearly all behaviors have inherited influences. Association studies that correlate SNP patterns with particular symptoms and analysis of specific mutations that are present exclusively in individuals with a particular behavior are newer approaches that identify specific genes that contribute to behavioral variants and abnormalities.

Behavioral genetics is, by definition, a study of nervous system variation and function, particularly of the brain. The human brain weighs about 3 pounds and resembles a giant gray walnut, but with the appearance and consistency of pudding. It consists of 100 billion nerve cells, or neurons, and at least a trillion other types of cells called

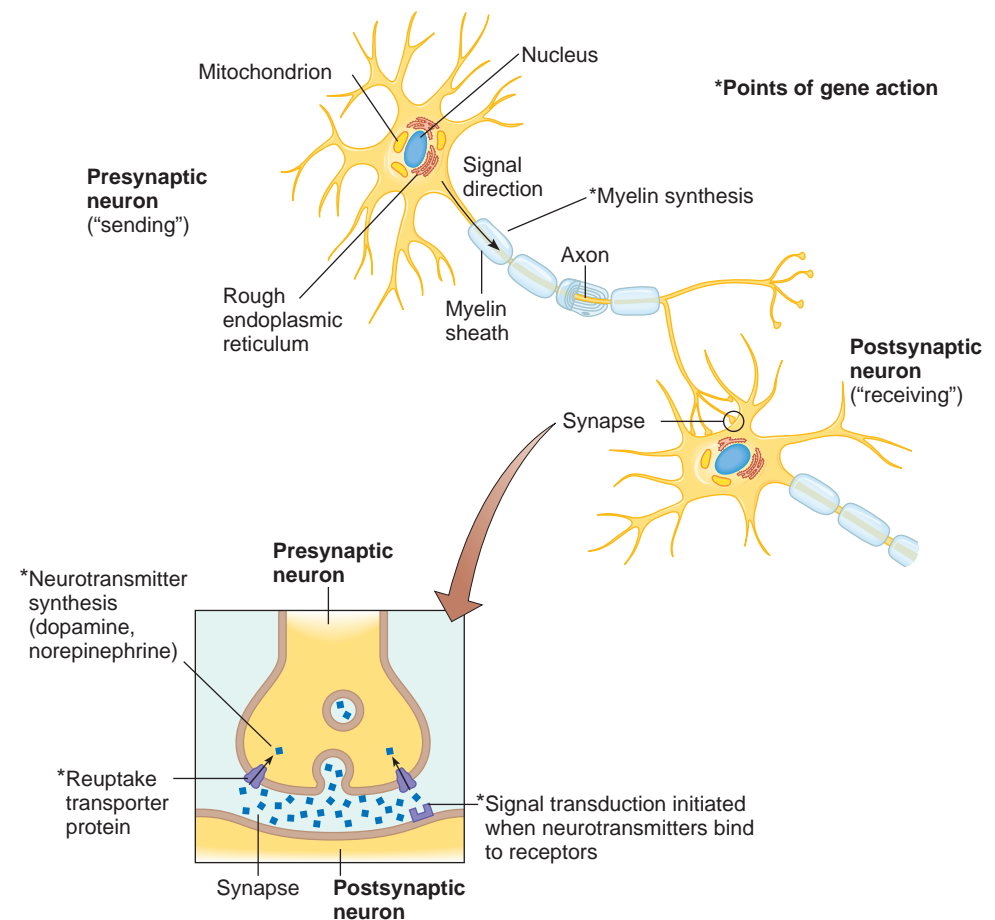
neuroglia. Once thought to provide little more than scaffolding, neuroglial cells guide the development and movements of neurons in the embryo, and produce nerve growth factors that continue to nurture brain neurons throughout life. Neuroglial cells are essential, and, unlike neurons, they can divide. Brain tumors arise in neuroglial cells, and they are among the fastest-growing cancers.

Connectivity and interaction are what make the brain a coordinated, functioning organ that controls all of the body. Branches from each of the 100 billion neurons in the brain form close associations, called synapses, with 1,000 to 10,000 other neurons. Neurons communicate across these tiny spaces using chemical signals called neurotransmitters. The neurons

form networks and clusters that oversee broad functions such as sensation and perception, memory, reasoning, and muscular movements.

Genes control the production and distribution of neurotransmitters. **Figure 8.1** indicates the points where genes control the sending and receiving of nervous system information. Enzymes oversee the synthesis of neurotransmitters and their transport from the sending (presynaptic) neuron across the synapse to receptors on the receiving (postsynaptic) neuron.

Proteins called transporters ferry neurotransmitters from sending to receiving neurons. For example, mutations that impair a transporter for the neurotransmitter serotonin cause one form of autism. Genes also control the synthesis of myelin, a



**Figure 8.1 Neurotransmission.** Many genes that affect behavior produce proteins that affect neurotransmission, which is sending a signal from one neuron to another across a synapse via a neurotransmitter molecule.



## Blaming Genes

It has become fashionable to blame genes for our shortcomings. A popular magazine's cover shouts "Infidelity: It May Be in Our Genes," advertising an article that actually has little to do with genetics. When researchers identify a gene that plays a role in fat metabolism, people binge on chocolate and forsake exercise, reasoning that if obesity is in their genes, they can't prevent it. Some behaviors have even been blamed on a gene for "thrill seeking" (**figure 1**).

Behavioral genetics has a checkered past. Early in the twentieth century, it was part of eugenics, the attempt to improve a population's collection of genes, or gene pool. The horrific experiments and exterminations the Nazis performed in the name of eugenics turned many geneticists away from studying the biology of behavior. Social scientists then dominated the field, attributing many behavioral disorders to environmental influences. For example, autism and schizophrenia were blamed on "adverse parenting." By the 1960s, with a clearer concept of the gene, biologists reentered the debate. Today, researchers can identify genotypes that predispose a person to developing a clearly defined behavior.

Even in the rare instances when a behavior is associated with a particular DNA variant, environmental influences remain important. Consider a study of a Dutch family that had "a syndrome of borderline mental retardation and abnormal behavior." Family members had committed arson, attempted rape, and engaged in exhibitionism. Researchers found a mutation in a gene that made biological sense:

alteration of a single DNA base in the X-linked gene encoding an enzyme, monoamine oxidase A (MAOA), rendered the enzyme nonfunctional. This enzyme normally catalyzes reactions that metabolize dopamine, serotonin, and norepinephrine, and it is therefore important in conducting nerve messages. Other studies confirmed that some combinations of alleles of the MAOA gene correlate with highly aggressive behavior, and others with calmer temperaments. Perhaps the inherited enzyme deficiency causes slight mental impairment, and this interferes with ability to cope with certain frustrating situations,

resulting in violence. Hence, the argument returns once again to how genes interact with the environment.

The study on the Dutch family was publicized and applied to other situations. An attorney tried to use the "MAOA deficiency defense" to free a client from execution for committing murder. A talk-show host suggested that people who had inherited the "mean gene" be sterilized so they couldn't pass on the tendency. This may have been meant as a joke, but it is frighteningly close to the eugenics practiced early in the last century, revisited in chapter 16.



**Figure 1 A thrill-seeking gene?** These air surfers were dropped from a helicopter over a mountain. Does a gene variant make them seek thrills?

fatty substance that coats neuron extensions called axons. Myelin coats and insulates the neuron, which speeds neurotransmission. At least three different genes involved in the synthesis of myelin can cause schizophrenia. Signal transduction is also a key part of the function of the nervous system (see figure 2.19). Therefore, candidate genes for the inherited components of a variety of mood

disorders and mental illnesses—as well as of normal variations in temperament and personality—affect neurotransmission and signal transduction.

Identifying the inherited and environmental contributors to a behavioral disorder is very challenging, because the same collections of symptoms may have different causes. Typically, traditional methods identify an

inherited component to a behavior, and further studies identify and describe candidate genes. For chronic fatigue syndrome, for example, heritability estimates range from 19 to 51 percent, depending upon how the syndrome is described. Several twin studies indicate that chronic fatigue syndrome is considerably more likely to affect both members of MZ (identical) twin pairs than



DZ (fraternal) twin pairs. Genetic studies then identified the three genes that have variants that contribute to chronic fatigue syndrome.

Deciphering genetic components of most behavioral disorders is not straightforward. Investigating causes of autism (OMIM 209850) illustrates the difficulty of reconciling empiric, adoptee, and twin data with molecular methods.

Autism is a spectrum of disorders of communication. An individual with autism does not usually speak or interact with others and is comfortable only with restricted or repetitive behaviors. He or she has difficulty with relationships and does not cope well with change. A mild form of autism, Asperger syndrome, does not impair language ability. The general population incidence of autism is only 10 to 12 per 10,000 (<0.1 percent), but for a sibling of a person with the condition, risk of recurrence is 2 to 4 percent. Twin studies indicate 90 percent heritability. Studies of families that have several members with autism implicate 4 to 6 major genes and 20 to 30 others that also contribute, perhaps with groups of specific alleles increasing risk. Subtypes of autism may differ by whether they tend to affect males or females or have an early or late onset.

Another way to look at autism is as a composite of the three main symptoms: impaired communication, social problems, and rigid/repetitive behaviors. Studies of 2,000 pairs of 7- and 8-year-old twins considered these three components separately and found high heritability for each, suggesting that different genes may determine the three major symptoms. Autism is not a simple, or likely single, disorder! However, once causative and/or susceptibility alleles for autism have been identified and adequately validated in large studies, perhaps very young children can be screened and early interventions prevent symptoms from developing or minimize them.

Investigating the genetics of behavior is more challenging than understanding a disorder in which an abnormal protein causes physical symptoms. Many behavioral disorders have symptoms in common, but many of them fall within the range of normal behavior. For example, whether extreme anxiety is warranted depends upon the situation, and different individuals may react with different intensity to the same situation. Another complication of studying the genetics of behavior is that reporting of

**Table 8.1**  
**Prevalence of Behavioral Disorders in the U.S. Population**

Condition	Prevalence (%)
Alzheimer disease	4.0
Anxiety	8.0
Phobias	2.5
Posttraumatic stress disorder	1.8
Generalized anxiety disorder	1.5
Obsessive compulsive disorder	1.2
Panic disorder	1.0
Attention deficit hyperactivity disorder	2.0
Autism	0.1
Drug addiction	4.0
Eating disorders	3.0
Mood disorders	7.0
Major depression	6.0
Bipolar disorder	1.0
Schizophrenia	1.3

Source: Psychiatric Genomics Inc., Gaithersburg, MD. The information was collated from the Surgeon General's 1999 Report on Mental Health.

symptoms may be highly subjective. A person can also copy someone's unusual behavior, not realizing it is unusual. However, being too quick to assign a genetic cause to a behavior can be dangerous, as Bioethics: Choices for the Future, "Blaming Genes", page 153, discusses.

The examples that follow begin with traditional evaluation of siblings, adoptees, and twins, and conclude with a look at genes that underlie, contribute to, or influence behaviors. Identifying human behavioral genes may make it possible to subtype mental disorders so that individualized treatment can begin early. **Table 8.1** lists the prevalence of some behavioral disorders.

### Key Concepts

1. Most behavioral traits and disorders are fairly common, polygenic, and multifactorial.
2. Traditional methods to estimate the genetic contribution to a behavior include empiric risk estimates and adoptee and twin studies. Association studies and candidate gene analyses are now extending these data.
3. Behavioral disorders are difficult to study because symptoms overlap and behaviors can be imitated.

## 8.2 Eating Disorders

When 22-year-old gymnast Christy Henrich was buried on a Friday morning in July 1994, she weighed 61 pounds (**figure 8.2**). Three weeks earlier, she had weighed 47 pounds. Christy suffered from anorexia nervosa, a psychological disorder that is fairly common among professional athletes. The person perceives herself or himself as obese, even when obviously not, and intentionally starves. Christy's decline began when a judge at a gymnastics competition told her that at 90 pounds, she was too heavy to make the U.S. Olympic team. From then on, her life consisted of starving, exercising, and taking laxatives to hasten weight loss.

For economically advantaged females in the United States, the lifetime risk of developing anorexia nervosa is 0.5 percent. Anorexia has the highest risk of death of any psychiatric disorder—15 to 21 percent. The same population group has a lifetime risk of 2.5 percent of developing another eating disorder, bulimia. A person with bulimia eats huge amounts but exercises and vomits to maintain weight.

Five to 10 million people in the United States have eating disorders. About 10 percent of them are male. One survey of eight-year-old boys revealed that more than a



**Figure 8.2 Eating disorders.**

World-class gymnast Christy Henrich died of complications of anorexia nervosa in July 1994. In this photo, taken eleven months before her death, she weighed under 60 pounds. Concern over weight gain propelled her down the path of this deadly psychiatric illness.

third of them had attempted to lose weight. In an eating disorder called muscle dysmorphia, boys and young men take amino acid supplements to bulk up. Just as the person with anorexia looks in a mirror and sees herself as too large, a person with muscle dysmorphia sees himself as too small.

Because eating disorders were once associated almost exclusively with females, most available risk estimates exclude males. Twin studies reveal a considerable genetic component, with heritability ranging from 0.5 to 0.8. Studies of eating disorders that recur in siblings can be difficult to interpret. Is a young girl imitating her older sister by starving because genes predispose her to develop an eating disorder, or because she wants to be like her sister?

Genes that encode proteins that control appetite are candidate genes for developing eating disorders, such as those that regulate the neurotransmitters dopamine and serotonin (see table 7.8). It will be interesting to learn which genes affect body image, and how they do so.

In association studies, whole genome scans associate SNP patterns with eating

disorders, as described in chapter 7. One biotechnology company is cataloging 60 SNP sites among the genomes of 2,000 individuals representing 600 families where more than one member has anorexia nervosa. The researchers are seeking a SNP pattern—if there is one—that appears mostly among individuals who have anorexia. SNP maps that highlight chromosome regions that correlate to a predisposition to develop anorexia may guide discovery of more genes whose protein products affect appetite.

## Key Concepts

1. Eating disorders are common.
2. Twin and heritability studies indicate a high genetic contribution to eating disorders.
3. Genes whose products control appetite or regulate certain neurotransmitters may elevate the risk of developing an eating disorder.

## 8.3 Sleep

Sleep has been called “a vital behavior of unknown function,” and, indeed, without sleep, animals die. We spend a third of our lives in this mysterious state.

Genes influence sleep characteristics. When asked about sleep duration, schedule, quality, nap habits, and whether they are “night owls” or “morning people,” MZ twins report significantly more in common than do DZ twins. This is true even for MZ twins separated at birth. Twin studies of brain wave patterns through four of the five stages of sleep confirm a hereditary influence. The fifth stage, REM sleep, is associated with dreaming and therefore may reflect the input of experience more than genes.

## Narcolepsy

Researchers discovered the first gene related to sleep in 1999, for a condition called “narcolepsy with cataplexy” in dogs. Humans have the disorder (OMIM 161400), but it is rarely inherited as a single-gene trait—it is more often polygenic requiring an environmental trigger.

A person (or dog) with narcolepsy falls asleep suddenly several times a day. Extreme daytime sleepiness greatly disrupts daily

activities. People with narcolepsy have a tenfold higher rate of car accidents. Another symptom is sleep paralysis, the inability to move for a few minutes after awakening. The most dramatic manifestation of narcolepsy is cataplexy. During these short and sudden episodes of muscle weakness, the jaw sags, the head drops, knees buckle, and the person falls to the ground. This often occurs during a bout of laughter or excitement—which can be quite disturbing both for the affected individual and bystanders. People with narcolepsy and cataplexy cannot participate in even the most mundane of activities for fear of falling and injuring themselves. Narcolepsy with cataplexy affects only 0.02 to 0.06 percent of the general populations of North America and Europe, but the fact that it is much more common in certain families suggests a genetic component.

Studies on dogs led the way to discovery of a human narcolepsy gene. In 1999, Emmanuel Mignot and his team at Stanford University identified mutations in a gene that encodes a receptor for a neuropeptide called hypocretin (OMIM 602358). In Doberman pinschers and Labrador retrievers, the receptor does not arrive at the cell surfaces of certain brain cells. As a result, the cells cannot receive signals to promote a state of awakesness. Dachshunds have their own mutation—they make a misshapen, nonfunctional receptor. **Figure 8.3** shows a still frame of a film that Mignot made of narcoleptic dogs playing. Suddenly, they all collapse! A minute later, they get up and resume their antics. “You can’t make dogs laugh, but you can make them so happy that they have attacks,” says Mignot. To induce a narcoleptic episode in puppies, he lets them play with each other. He feeds older dogs meat, which excites them so much that they can take a while to finish a meal because they fall down in delight so often. Getting narcoleptic dogs to breed is difficult, too, for sex is even more exciting than play or food!

A year earlier, Masahi Yanagisawa, at the University of Texas Southwestern Medical Center in Dallas, discovered a protein called orexin, but thought it only sent signals to eat. Yanagisawa’s orexin turned out to bind Mignot’s hypocretin receptor. Yanagisawa bred mice that lacked the orexin gene, and then noticed something odd while watching the animals feed at night—the rodents suddenly fell down fast asleep! Researchers are



**Figure 8.3 Letting sleeping dogs lie.** These Doberman pinschers have inherited narcolepsy. They suddenly fall into a short but deep sleep while playing. Research on dogs with narcolepsy led to the discovery of the gene in humans.

now trying to figure out how one molecule controls feeding as well as wakefulness. The hypocretin/orexin receptor gene, found on dog chromosome 12, is on human chromosome 6. The brains of humans with narcolepsy and cataplexy are remarkably deficient in hypocretin/orexin. A narcolepsy drug might mimic the missing molecule.

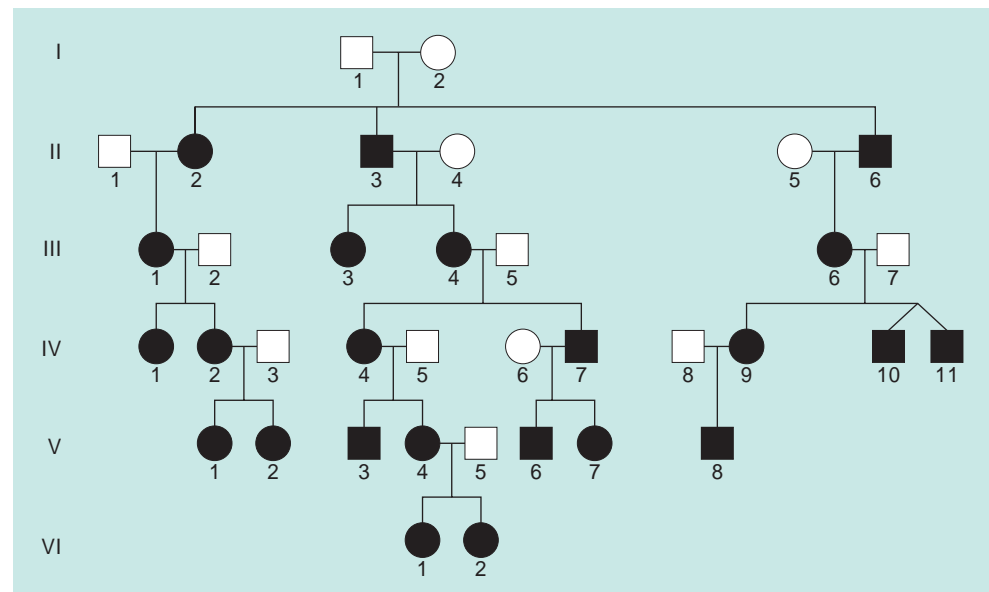
### Familial Advanced Sleep Phase Syndrome

A Utah family with many members who have an unusual sleep pattern revealed a “biological clock” gene. The subjects have familial advanced sleep phase syndrome (FASPS) (OMIM 604348)—they promptly fall asleep at 7:30 each night and awaken suddenly at 4:30 a.m. The family is a geneticist’s dream—a distinctive phenotype, many affected individuals, and a clear mode of inheritance (autosomal dominant) (figure 8.4).

The odd sleepers in the Utah family have a mutation in a gene on chromosome 2 called *period*. It has counterparts in golden hamsters and fruit flies that disrupts their sleep-wake cycles. Humans with the condition have a single DNA base substitution in the gene. This mutation prevents the encoded protein from binding a phosphate chemical group, which it must do to pass on the signal that synchronizes the sleep-wake cycle with daily sunrise and sunset.

Other genes and environmental input influence sleep behavior. Other families

with FASPS have mutations in different genes. Therefore, the condition is genetically heterogeneous. Daily rhythms such as the sleep-wake cycle are set by cells that form a “circadian pacemaker” in a part of the brain called the suprachiasmatic nuclei. Genes are expressed in these cells in response to light or dark in the environment. Understanding how genes influence the sleep-wake cycle may lead to new treatments for jet lag, insomnia, and a form of advanced sleep phase syndrome that is common among older individuals.



**Figure 8.4 Inheritance of a disrupted sleep-wake cycle.** This partial pedigree depicts affected members of a large family with an autosomal dominant form of familial advanced sleep phase syndrome.

## Key Concepts

1. Twin studies on sleep habits indicate a high heritability.
2. A single gene causes narcolepsy in dogs and humans.
3. A family with a very unusual sleep-wake cycle revealed a “clock” gene in humans.

## 8.4 Intelligence

Intelligence is a vastly complex and variable trait that is subject to many genetic and environmental influences, and also to great subjectivity. Sir Francis Galton, a half first cousin of Charles Darwin, investigated genius, which he defined as “a man endowed with superior faculties.” He identified successful and prominent people in Victorian-era English society, and then assessed success among their relatives. In his 1869 book, *Hereditary Genius*, Galton wrote that relatives of eminent people were more likely to also be successful than people in the general population. The closer the blood relationship, he concluded, the more likely the person was to succeed. This, he claimed, established a hereditary basis for intelligence.

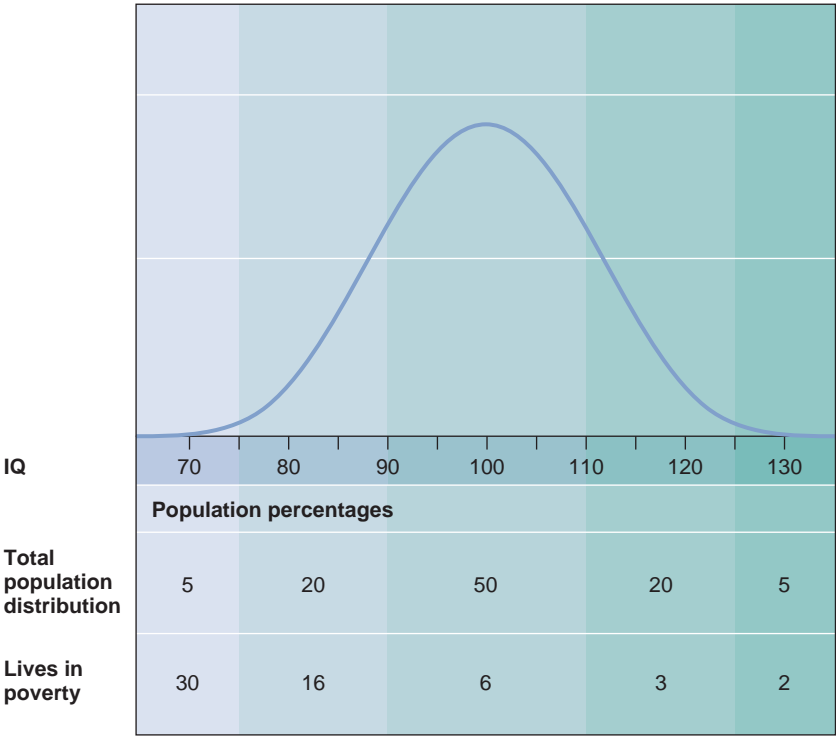


Definitions of intelligence vary. In general, intelligence refers to the ability to reason, learn, remember, connect ideas, deduce, and create. The first intelligence tests, developed in the late nineteenth century, assessed sensory perception and reaction times to various stimuli. In 1904, Alfred Binet at the Sorbonne developed a test with verbal, numerical, and pictorial questions, used to predict the success of developmentally disabled youngsters in school. The test was subsequently modified at Stanford University to assess white, middle-class Americans. An average score on this “intelligence quotient,” or IQ test, is 100, with two-thirds of all people scoring between 85 and 115 in a bell curve or normal distribution (**figure 8.5**). An IQ between 50 and 70 is considered mild mental retardation, and below 50, severe mental retardation.

IQ has been a fairly accurate predictor of success in school and work. However, low IQ also correlates with many societal situations, such as poverty, a high divorce rate, failure to complete high school,

incarceration (males), and having a child out of wedlock (females). In 1994, a book called *The Bell Curve* asserted that because certain minorities are overrepresented in these groups, they must be of genetically inferior intelligence and that is why they are prone to suffering social ills. It was a controversial thesis, to put it mildly.

The IQ test consists of short exams that measure verbal fluency, mathematical reasoning, memory, and spatial visualization skills. Because people tend to earn similar scores in all these areas, psychologists hypothesized that a general or global intelligence ability, called “g,” must underlie the four basic skills that IQ encompasses. Statistical analysis indeed reveals one factor that accounts for general intelligence. In contrast, similar analysis of personality reveals five contributing factors. The g value is the part of IQ that accounts for differences between individuals based on a generalized intelligence, rather than on enhanced opportunities such as attending classes to boost test-taking skills.



**Figure 8.5 Success and IQ.** IQ scores predict success in school and the workplace in U.S. society. The bell curve for IQ indicates that most people fall in the 85 to 115 range, shown in the total population distribution. However, when the population is stratified economically, those living in poverty tend to have lower IQs. Cause and effect are unclear.

**Table 8.2**  
**Heritability of Intelligence Changes Over Time**

Age Group	Heritability
Preschoolers	0.4
Adolescents	0.6
Adults	0.8

Environment does not seem to play too great a role in IQ differences. Evidence includes the observation that IQ scores of adoptees, with time, become closer to those of their biological parents than to those of their adoptive parents. Heritability studies also reveal a declining environmental impact with age (**table 8.2**). This makes sense. As a person ages, he or she has more control over the environment, so genetic contributions to intelligence become more prominent.

Researchers have long recognized a genetic explanation for intelligence differences because nearly all syndromes that result from abnormal chromosomes include some degree of mental retardation. The search for single genes that contribute to intelligence differences focuses on proteins that control neurotransmission. For example, a certain variant of a gene encoding neural cellular adhesion molecule (N-CAM) correlates strongly with high IQ. Perhaps this gene variant eases certain neural connections that enhance learning ability. A section of chromosome 4 harbors intelligence-related genes.

**Key Concepts**

1. Intelligence is the use of mental skills to complete complex tasks or solve problems.
2. IQ assesses verbal fluency, mathematical reasoning, memory, and spatial visualization ability.
3. The “g” value measures a general intelligence factor that represents the inherited portion of IQ.
4. Environment has less of an influence on intelligence as a person ages.
5. Individual genes affect intelligence.

## 8.5 Drug Addiction

Drug addiction is compulsively seeking and taking a drug despite knowing its adverse effects. Drug addiction has two identifying characteristics: tolerance and dependence. Tolerance is the need to take more of the drug to achieve the same effects as time goes on. Dependence is the onset of withdrawal symptoms upon stopping the use of the drug. Both tolerance and dependence contribute to the biological and psychological components of craving the drug. The behavior associated with drug addiction can be extremely difficult to break.

Drug addiction produces long-lasting brain changes. Craving and high risk of relapse remain even after a person has abstained for years. Heritability is 0.4 to 0.6, with a two- to threefold increase in risk among adopted individuals who have one affected biological parent. Twin studies also indicate an inherited component to drug addiction.

Brain imaging techniques have localized the “seat” of drug addiction in the brain by highlighting the cell surface receptors that bind neurotransmitters when a person craves the drug. The brain changes that contribute to addiction occur in parts called the nucleus accumbens, the prefrontal cortex, and the ventral tegmental area, which are part of a larger set of brain structures called the limbic system (**figure 8.6**). The effects of cocaine seem to be largely confined to the nucleus accumbens, whereas alcohol affects the prefrontal cortex.

Although the specific genes and proteins that are implicated in addiction to different substances may vary, several general routes of interference in brain function are at play. Proteins involved in drug addiction are those that

- are part of the production lines for neurotransmitters, such as enzymes;
- form reuptake transporters, which remove excess neurotransmitter from the synapse;
- form receptors on the postsynaptic neuron that are activated or inactivated when specific neurotransmitters bind;
- are part of the signal transduction pathway in the postsynaptic neuron.

Abused drugs are often plant-derived chemicals, such as cocaine, opium, and tetrahydrocannabinol (THC), the main active ingredient in marijuana. These substances bind to receptors on human neurons, which indicates that our bodies have versions of these substances. The human equivalents of the opiates are the endorphins and enkephalins, and the equivalent of THC is anandamide. The endorphins and enkephalins relieve pain. Anandamide modulates how brain cells respond to stimulation by binding to neurotransmitter receptors on presynaptic (sending) neurons. In contrast, neurotransmitters bind to receptors on postsynaptic neurons.

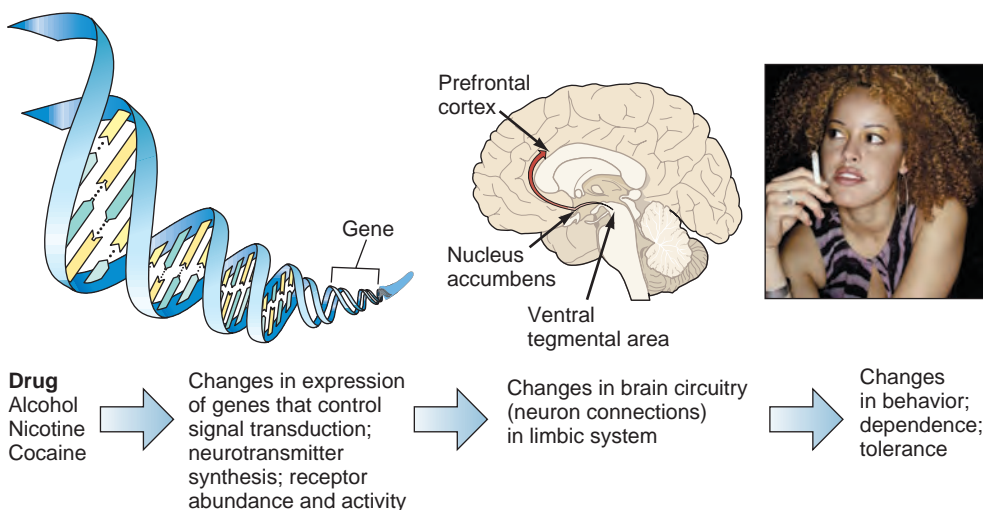
Amphetamines and LSD produce their effects by binding to receptors on neurons

that normally bind neurotransmitters called trace amines. Trace amines are found throughout the brain at low levels, compared to the more abundant neurotransmitters such as dopamine and serotonin. LSD causes effects similar to the symptoms of schizophrenia (see section 8.7), suggesting that the trace amine receptors, which are proteins, may be implicated in the illness.

DNA microarray technology is identifying specific gene variants that people with addictions share, and also indicating which genes are active when a drug is craved or taken. For example, people who are homozygous for the *A1* allele of the dopamine D(2) receptor gene are overrepresented among people with alcoholism and other addictions. In one very large study, a genome-wide scan of more than 100,000 gene variants among people with alcoholism compared to people without alcoholism identified 51 chromosomal regions that may include genes that control craving for alcohol, and perhaps other substances.

### Key Concepts

1. Drug addiction is dependency on a drug despite knowing the activity is harmful.
2. Structures in the limbic system are directly involved in drug addiction.
3. A candidate gene for addiction encodes the dopamine D(2) receptor.
4. DNA microarray studies reveal many genes whose protein products affect neurotransmission, signal transduction, and myelin deposition on neurons.



**Figure 8.6 The events of addiction.** Addiction is manifest at several levels: at the molecular level, in neuron-neuron interactions in the brain, and in behavioral responses.

## 8.6 Mood Disorders

Identifying genetic and environmental influences on mood disorders is challenging because mood changes may appear to be extremes of normal behavior. For example, a person who has previously been happy but inexplicably becomes lethargic and sad and no longer enjoys favorite activities may be diagnosed with major depressive disorder (MDD). A person with the same symptoms in response to the death of a loved one may experience extended grief and loss, but not clinical depression. Context is important.

The two most prevalent mood disorders are major depressive disorder and bipolar affective disorder (also called bipolar disorder or manic-depression). MDD affects 6 percent of the U.S. population at any given time, and affects more women than men. Lifetime risk of MDD for the general population is 5 to 10 percent. Often depression is chronic, with acute episodes provoked by stress. It is a serious illness. Fifteen percent of people hospitalized for severe, recurrent depression ultimately end their lives. About half of all people who experience a depressive episode will suffer others. Half of affected individuals do not seek medical help, and among those who do, a third do not respond to drug therapy; those who do may relapse when they discontinue taking an effective drug. Electroconvulsive (shock) therapy can fairly quickly help some patients who are drug-resistant. For many people, antidepressant treatment is very helpful if paired with psychotherapy.

Bipolar disorder is much rarer than MDD, affecting 1 percent of the population and with a general population lifetime risk of 0.5 to 1.0 percent. With this disorder, weeks or months of depression alternate with periods of mania, when the person is hyperactive and restless, and may experience a rush of ideas and excitement. Ideas may be fantastic, and behavior reckless. For example, a person who is normally quiet and frugal might, when manic, suddenly make large monetary donations

and spend lavishly—very out-of-character behavior. In one subtype of bipolar disorder, the “up” times are termed hypomania, and they seem more a temporary reprieve from the doldrums than the bizarre behavior of full mania. Bipolar disorder with hypomania may appear to be depression. This is an important distinction because different drugs are used to treat depression and bipolar disorder.

A likely cause of depression, and possibly of bipolar disorder too, is deficiency of the neurotransmitter serotonin, which affects mood, emotion, appetite, and sleep. Levels of norepinephrine, another type of neurotransmitter, are important as well. The abnormality occurs in transporter proteins that ferry neurotransmitters from the synapse to “reuptake pumps” in the presynaptic neuron. In depression, overactive or overabundant transporters deplete neurotransmitter. Drugs called selective serotonin reuptake inhibitors (SSRIs) treat depression by preventing presynaptic neurons from admitting serotonin from the synapse, leaving more of it available to stimulate the postsynaptic cell (**figure 8.7**). This action apparently offsets the neurotransmitter deficit. Other antidepressants target norepinephrine or both serotonin and norepinephrine.

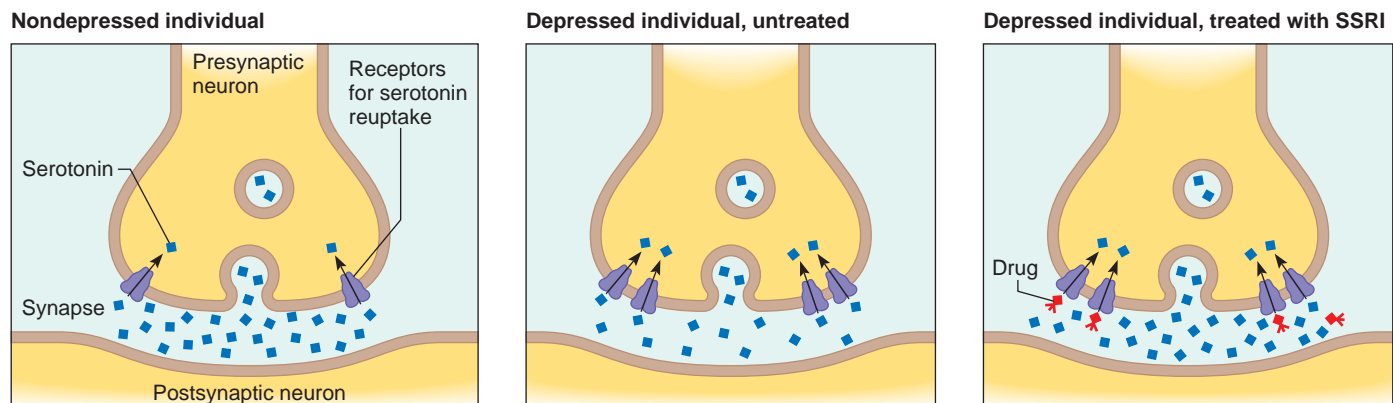
SSRIs may begin to produce effects after one week, often enabling a person with moderate or severe depression to return to some activities, but full response can take up to eight weeks. DNA microarray tests in

development can predict which drugs are most likely to help a particular patient with the fewest side effects.

Assigning specific genes or chromosomal regions to bipolar disorder has lagged behind efforts for depression. Over the past thirty years, linkage studies in large families, or association studies in very isolated populations such as the Amish, have indicated several genome regions that may harbor genes that predispose to bipolar disorder. Evidence is more specific for depression, pointing strongly toward malfunction of the serotonin transporter coupled with an environmental trigger. For bipolar disorder, evidence is insufficient to support either a model of many genes, each with an additive effect (polygenic); roles for several genes, each with a large and independent effect (genetic heterogeneity); or different genes interacting and controlling each other’s expression (epistasis).

## Key Concepts

1. Major depressive disorder is more common than bipolar disorder, and is likely caused by deficits of serotonin, norepinephrine, or both.
2. Bipolar disorder is associated with several chromosomal sites, and its genetic roots are difficult to isolate.



**Figure 8.7 Anatomy of an antidepressant.** Selective serotonin reuptake inhibitors (SSRIs) are antidepressant drugs that block the reuptake of serotonin, leaving more of the neurotransmitter in synapses. This corrects a neurotransmitter deficit that presumably causes the symptoms. Overactive or overabundant reuptake receptors can cause the deficit. The precise mechanism of SSRIs is not well understood, and the different drugs may work in slightly different ways.



8.7 Schizophrenia

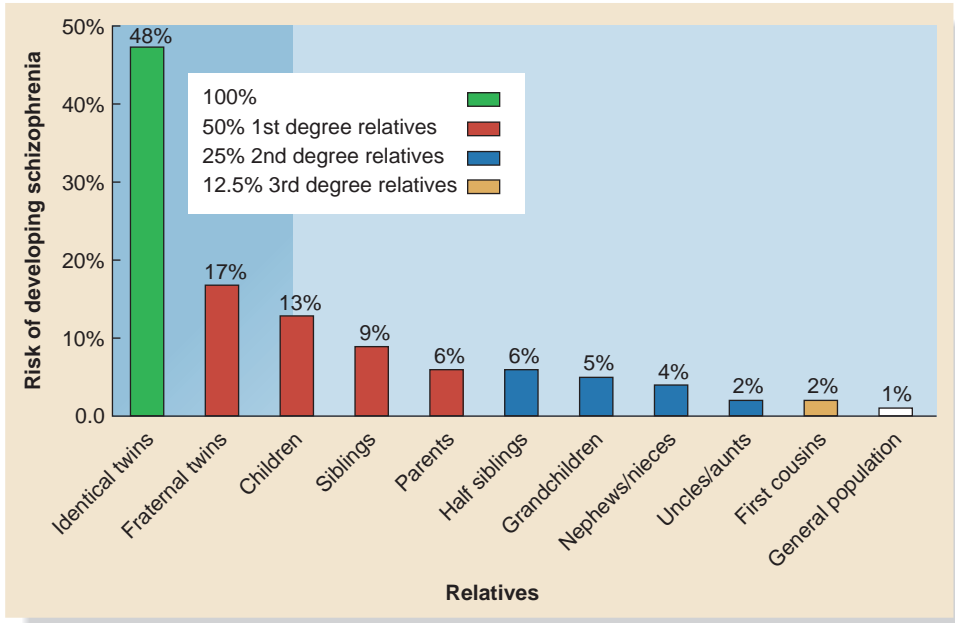
Schizophrenia is a debilitating loss of the ability to organize thoughts and perceptions, which leads to a withdrawal from reality. Various forms of the condition together affect 1 percent of the world’s population. Ten percent of affected individuals commit suicide.

Identifying genetic contributions to schizophrenia illustrates the difficulties in analyzing a behavioral condition. Some of the symptoms are also associated with other illnesses; many genes cause or contribute to it; and several environmental factors may mimic the condition.

The first signs of schizophrenia often affect thinking. In late childhood or early adolescence, a person might develop trouble paying attention in school, and learning may become difficult as memory falters and information-processing skills lag. Symptoms of psychosis begin between ages 17 and 27 for males and 20 and 37 for females, including delusions and hallucinations—sometimes heard, sometimes seen. A person with schizophrenia may hear a voice giving instructions. What others perceive as irrational fears, such as being followed by monsters, are very real to the person with schizophrenia. Meanwhile, cognitive skills continue to decline. Speech reflects the garbled thought process; the person skips from topic to topic with no obvious thread of logic, or displays inappropriate emotional responses, such as laughing at sad news. Artwork by a person with schizophrenia can display the characteristic fragmentation of the mind (figure 8.8). (Schizophrenia



**Figure 8.8 Schizophrenia alters thinking.** People with schizophrenia communicate the disarray of their thoughts in characteristically disjointed drawings.



**Figure 8.9 Schizophrenia has inherited and environmental components.** Percentages in the graph legend box refer to percentage of shared genes within each group.  
Source: Maher, Brendan A., “The Infection Connection in Schizophrenia.” *The Scientist*, November 2003, p. 30.

means “split mind,” but it does not cause a split or multiple personality.)

The course of schizophrenia often plateaus (evens out) or becomes episodic. It is not a continuous decline, as is the case for dementia. Schizophrenia is frequently misdiagnosed as depression or bipolar affective disorder. However, schizophrenia primarily affects thinking; these other conditions mostly affect mood. It is a very distinctive mental illness.

A heritability of 0.8 and empiric risk values indicate a strong role for genes in causing schizophrenia (figure 8.9). Because most of the symptoms are behavioral, however, it is possible to develop some of them—such as disordered thinking—from living with and imitating people who have schizophrenia. Although concordance is high, a person who has an identical twin with schizophrenia has a 52 percent chance of *not* developing schizophrenia. Therefore, the condition has a significant environmental component, too.

Researchers hypothesize that dozens of genes may interact with an environmental trigger or triggers to cause schizophrenia. Genomewide screens of families with schizophrenia reveal at least twenty-four sites where affected siblings share alleles

much more often than the 50 percent of the time that Mendel’s first law predicts.

Several environmental factors may increase the risk of developing schizophrenia (table 8.3). One powerful candidate is infection during pregnancy. When a pregnant woman is infected, her immune system bathes the brain of the embryo or fetus with cytokines (molecules that function in signal transduction) that subtly alter brain development.

The idea that maternal infection can sow the seeds for schizophrenia first grew out of observations on the seasonality of birth dates. As far back as 1929, researchers noted

Table 8.3
Environmental Risk Factors for Schizophrenia
Maternal malnutrition
Infection by Borna virus
Fetal oxygen deprivation
Obstetric or birth complication
Psychoactive drug use (phencyclidine)
Traumatic brain injury
Herpes infection at time of birth

an unusually high percentage of people with schizophrenia were born in the winter. One surge in cases dates back to the winter of the 1957 influenza pandemic. More recent studies that consult medical records or blood samples to confirm flu cases support the link between prenatal exposure to flu virus or the mother’s immune response and schizophrenia—a few are discussed in an end-of-chapter question. The influenza virus can cross the placenta and alter brain cells.

Not all studies, however, link schizophrenia to winter births. A small association also occurs with births in June or July. To explain the exception, researchers suggest there are two subtypes of schizophrenia. The “deficit” subtype, characterized by “negative” symptoms such as lack of emotion, speech, facial expressions and socialization, correlates to a summer birth. The “nondeficit” subtype, with paranoia, hallucinations, delusions, and disordered thinking, is more often associated with winter births.

Behavioral traits have been much more difficult to describe, categorize, and attribute to genetic and/or environmental influences than other characteristics. **Table 8.4** lists the heritabilities and candidate genes for the behavioral traits and conditions discussed in this chapter.

Disorders that affect our minds are at the forefront of whole-genome analysis. A public-private partnership called the Genetic Association Information Network is currently comparing the genomes of 1,000 to 2,000 healthy volunteers with

Table 8.4 Review of Behavioral Traits and Disorders		
Condition	Heritability	Candidate Genes
ADHD	0.80	Dopamine transporter Dopamine D(4) receptor (DRD4)
Eating disorders	0.50–0.80	Leptin Leptin transporter Leptin receptor Neuropeptide Y Melanocortin-4 receptor
Intelligence	0.80	Neural cellular adhesion molecule (N-CAM)
Addiction	0.40–0.60	Dopamine D(2) receptor (DRD2) Myelin synthesis
Depression	0.40–0.54	Serotonin synthesis, transporter, receptor Norepinephrine synthesis, transporter, receptor
Bipolar disorder	0.80	Serotonin transporter, receptor Monoamine oxidase A
Schizophrenia	0.80	Dopamine synthesis, transporter, receptor Glutamate synthesis, transporter, receptor

the genomes of equal numbers of volunteers who have any of six disorders chosen because of their impact on public health. Of those six, four are disorders that affect behavior: attention deficit hyperactivity disorder, depression, bipolar disorder, and schizophrenia. The goal is to use clues in genetic differences to develop new prevention and treatment approaches. Stay tuned!

Key Concepts

- Schizophrenia affects thinking and causes delusions and hallucinations, usually beginning in young adulthood.
- Studies have implicated several candidate genes and chromosomal regions as possible causes.
- A possible environmental influence may be prenatal exposure to the maternal immune system’s response to influenza.

# Summary

## 8.1 Genes Contribute to Most Behavioral Traits

- Most behavioral traits and conditions are multifactorial and are more common than most single-gene disorders.
- Candidate genes for behavioral traits and disorders affect neurotransmission and signal transduction.
- Analyzing behaviors is difficult because symptoms of different syndromes overlap,

study participants can provide biased information, and behaviors can be imitated.

## 8.2 Eating Disorders

- Eating disorders affect both sexes and are prevalent in the United States and other nations. Twin studies indicate high heritability.
- Candidate genes for eating disorders include those whose protein products

control appetite and the neurotransmitters dopamine and serotonin.

## 8.3 Sleep

- Twin studies and single-gene disorders that affect the sleep-wake cycle reveal a large inherited component to sleep behavior.
- A large family with familial advanced sleep phase syndrome enabled researchers to identify the first “clock” gene in humans.

The *period* gene enables a person to respond to day and night environmental cues.

## 8.4 Intelligence

8. Intelligence is difficult to define and measure. The general intelligence (g) value measures the inherited portion of IQ that may underlie population variance in IQ test performance.
9. Heritability for intelligence increases with age, suggesting that environmental factors are more important early in life.
10. Many chromosomal disorders affect intelligence, suggesting high heritability. A gene that encodes N-CAM is a candidate gene for intelligence.

## 8.5 Drug Addiction

11. Defining characteristics of drug addiction are tolerance and dependence. Addiction

produces stable brain changes, yet heritability is not as high as for some other behavioral conditions.

12. A candidate gene for drug addiction is the one that encodes the dopamine D(2) receptor. DNA microarray tests on gene expression in the brains of people with alcoholism help to identify genes involved in neurotransmission, signal transduction, cell cycle control, apoptosis, surviving oxidative damage, and myelination of neurons.

## 8.6 Mood Disorders

13. Major depressive disorder is relatively common and associated with deficits of serotonin and/or norepinephrine.
14. Bipolar affective disorder, which consists of depressive periods interspersed with times of mania or hypomania, is much

rarer. Several genes may raise the risk of developing this disorder.

## 8.7 Schizophrenia

15. Schizophrenia greatly disrupts the ability to think and perceive the world. Onset is typically in early adulthood, and the course is episodic or steady but not degenerative.
16. Empiric risk estimates and heritability indicate a large genetic component.
17. Many genes and environmental influences are associated with schizophrenia.

# Review Questions

1. What are the two major types of cells in the brain, and what do they do?
2. Why are behavioral traits nearly always multifactorial?
3. In general, what types of proteins are responsible for variations in behaviors?
4. What is the evidence that the Utah family with familial advanced sleep phase syndrome has a genetic condition rather than them all just becoming used to keeping weird hours?
5. Choose a behavior discussed in the chapter and identify the region of the brain that is affected.
6. Why is identifying a candidate gene only a first step in understanding how behavior arises and varies among individuals?
7. Describe three factors that can complicate the investigation of a behavioral trait.
8. Why does the heritability of intelligence decline with age? What were some of the prejudices that were part of studying the inheritance of intelligence?
9. What are the two defining characteristics of drug addiction?
10. Select a drug mentioned in the chapter and explain what it does to the nervous system.
11. Explain how an SSRI works.
12. Distinguish between the symptoms of bipolar disorder and schizophrenia.
13. What is the evidence that our bodies have their own uses for cocaine, THC, and opium?
14. What is an environmental factor that may influence the development of schizophrenia?

# Applied Questions

1. Studies indicate that in the United States, the incidence of autism has dramatically increased since 1990.
  - a. Does this finding better support a genetic cause or an environmental cause for autism?
  - b. What is a nongenetic factor that might explain the increased incidence of autism?
2. Abnormal serotonin levels contribute to or cause eating disorders, major depressive disorder, and bipolar disorder.
  - a. How can an abnormality in one type of neurotransmitter contribute to different disorders?
  - b. What other neurotransmitter is involved in more than one behavioral disorder?
3. How has DNA microarray technology changed the study of the genetics of behavior?
4. What might be the advantages and disadvantages of a SNP profile or other genotyping test done at birth that indicates whether a person is at high risk for developing a drug addiction?
5. The U.S. government prohibits recreational use of cocaine, marijuana, and opiates, which are physically addictive drugs, but not of alcohol and nicotine (cigarettes), also physically addictive. Do you think that the legal status of any of these drugs should be changed, and if so, how and why? What criteria, if any, should the government use in deciding which drugs to outlaw?



6. Do you think that having a genotype known to predispose a person to aggressive or violent behavior should be a valid legal defense? Cite a reason for your answer.
7. In some association studies of depression and bipolar disorder, correlations to specific alleles are only evident when participants are considered in subgroups based on symptoms. What might be a biological basis for this finding?
8. Many older individuals experience advanced sleep phase syndrome. Even though this condition is probably a normal part of aging, how might research on the Utah family with an inherited form of the condition help researchers develop a drug to help the elderly sleep through the night and awaken later in the morning?
9. What non-genetic factor might account for the overrepresentation of minority groups among people with low IQ scores in the United States?
10. A study found that the risk of schizophrenia among spouses of people with schizophrenia who have no affected blood relatives is 2 percent. What might this indicate about the causes of schizophrenia?
11. Wolfram syndrome (OMIM 222300) is a rare autosomal recessive disorder that causes severe diabetes, impaired vision, and neurological problems. Examinations of hospital records and self-reports reveal that blood relatives of Wolfram syndrome patients have an eightfold risk over the general population of developing serious psychiatric disorders such as depression, violent behavior, and suicidal tendencies. Can you suggest further experiments and studies to test the hypothesis that these mental manifestations are a less severe expression of Wolfram syndrome?
12. A study of 2,685 twin pairs showed that female MZ twins are six times as likely as female DZ twins to both have alcoholism. Does this finding suggest a large genetic or environmental component to alcoholism?

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 8** and **Web Activities** to find the website links needed to complete the following activities.

13. Consult the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Follow links and list three disorders

for which candidate genes have been identified. Discuss how those genes might cause the phenotypes.

## Case Studies

14. Microarrays have been used to identify genes that are expressed greatly above or below normal in various disorders that affect the brain. These include Huntington disease (see the Bioethics Box in chapter 4), Tourette syndrome, Down syndrome, multiple sclerosis, and stroke. Select one of these conditions and use the Web to learn about the symptoms. Then discuss the possible benefits and disadvantages of developing a blood test for patients based on gene expression profiles that would predict the disease before symptoms arise.
15. Robert Plomin, one of the best-known researchers who uses twins to study behavior, suggested in a recent paper that we abandon efforts to identify a genetic cause of autism.
  - a. What might be the basis for this statement?
  - b. What might be an advantage and a disadvantage of identifying genes that cause or contribute to autism?
16. Until the 1990s, bipolar disorder was thought not to affect children under age 18. Psychiatrists today maintain that fewer than 1 percent of children have bipolar disorder. However, the percentage of children being diagnosed with bipolar disorder has soared since 2000, along with the publication of many books written by parents of affected children, and appearances on TV talk shows of affected children and their parents.
  - a. Does this pattern of increasing disease incidence suggest a genetic or an environmental cause?
  - b. Suggest another explanation for the recent apparent increase in incidence of bipolar disorder in children.
  - c. Most children are diagnosed with bipolar disorder based on their answers to questions. What might a genetic diagnosis entail?
17. Studies link schizophrenia to starvation before birth. Specifically, the incidence of the disorder doubled among children whose mothers survived either the Dutch Hunger Winter of 1944–1945 due to Nazi occupation, or the Chinese famine of 1959–1961. Researchers hypothesize that

lack of folic acid damaged DNA repair systems, allowing mutations to accumulate that caused schizophrenia. What additional information is needed to evaluate this hypothesis?

18. On the island of Fiji, women once valued having a full figure. Then, in 1995, television arrived, and with it, the show “Melrose Place,” depicting skinny women as the ideal. Within three years, the incidence of eating disorders doubled, with a frightening percentage of the female population regularly vomiting on purpose so that they could continue to eat. Does this information argue more for a genetic or nongenetic cause of eating disorders? How could both influences contribute?
19. Frontotemporal dementia (FTD) affects 250,000 people in the United States. It usually begins in the forties through sixties, and is often misdiagnosed as the much more common Alzheimer disease. The abnormal behavior of FTD, however, is quite distinctive. It includes many socially unacceptable behaviors, such as cursing, shoplifting, impulse buying, inappropriate and/or excessive sexual behavior, poor financial judgment, recklessness, poor hygiene, sloppiness, and overeating. Although these symptoms are behavioral, this disorder is physical, because on autopsy, parts of the brain are very shrunk. Family studies have led to the identification of at least three causative genes.
 

Do you think that genetic tests should be developed to diagnose FTD, and if so, should these tests be used to legally defend affected individuals who commit crimes?
20. Researchers exposed mice that are genetically extra sensitive to mercury, as well wild type mice, to four common vaccines given to children. The vaccines contained a mercury-based preservative, thimerosal, that many parents of children with autism claim caused the autism. The exposed sensitive mice displayed autistic-like behaviors and showed brain changes. As a result, the media reported a link between autism and vaccines. What questions would you ask the researchers to determine whether they can extend their experimental results to people?

# A Second Look

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1. If a person has a parent who has chronic fatigue syndrome, what measures might he or she take to minimize the chance that the condition will develop?
2. What further studies are necessary to confirm the association between the three genes implicated in chronic fatigue syndrome?

3. What are some of the challenges in conducting adoptee, twin, or genetic studies of chronic fatigue syndrome?

Learn to apply the skills of a genetic counselor with an additional case found in the *Case Workbook in Human Genetics*:

Alcoholism



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# DNA Structure and Replication

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## ON THE MEANING OF GENE

To a biologist, *gene* has a specific definition—a sequence of DNA that tells a cell how to assemble amino acids into a particular protein. Once called by such colorful names as gemmules and stirps, plastidules and idioblasts, genes are packets of instructions passed from one cell generation to the next. Whatever its name, the gene has held different meanings across the landscape of time:

To folksinger Arlo Guthrie, *gene* means passing age 45 without showing signs of the Huntington disease that claimed his father, legendary folksinger Woody Guthrie.

To rare cats in New England, *gene* means extra toes.

To Adolph Hitler and others who have dehumanized those not like themselves, the concept of *gene* was abused to justify genocide.

To a smoker, a *gene* may mean lung cancer develops.

To a redhead in a family of brunettes, *gene* means an attractive variant.

To a woman whose mother and sisters had breast cancer, *gene* means escape from their fate—and survivor guilt.

To a lucky few, *gene* means a mutation that locks HIV out of their cells.

To people with diabetes, *gene* means safer insulin.

To an elephant that lives on the African savannah and one that lives in the forest, *gene* means that they cannot mate with each other.

To a forensic entomologist, *gene* means a clue to the identity of a criminal in the guts of maggots devouring a corpse.

To scientists-turned-entrepreneurs, *gene* means money.

Collectively, our genes mean that we are very much more alike than different from one another.



DNA is the genetic material. DNA bursts forth from this treated bacterial cell. The DNA in a human cell would unravel to nearly 6 feet, yet fit into a cell 6 millionths of a meter across.



“A genetic material must carry out two jobs: duplicate itself and control the development of the rest of the cell in a specific way,” wrote Francis Crick, codiscoverer with James Watson of the three-dimensional structure of DNA in 1953. Only DNA can do this.

## 9.1 Experiments Identify and Describe the Genetic Material

DNA was first described in the mid-eighteenth century, when Swiss physician and biochemist Friedrich Miescher isolated nuclei from white blood cells in pus on soiled bandages. In the nuclei, he discovered an unusual acidic substance containing nitrogen and phosphorus. He and others found it in cells from a variety of sources. Because the material resided in cell nuclei, Miescher called it *nuclein* in an 1871 paper; subsequently, it was called a nucleic acid. But few people appreciated the importance of Miescher’s discovery, because at the time, the study of heredity focused on the association between inherited disease and protein.

In 1902, English physician Archibald Garrod was the first to link human inheri-

tance and protein. He noted that people who had certain inborn errors of metabolism lacked certain enzymes. One of the first inborn errors that he described was alkaptonuria, the subject of the chapter 5 opening essay. Other researchers added evidence of a link between heredity and enzymes from other species, such as fruit flies with unusual eye colors and bread molds with nutritional deficiencies. Both organisms had absent or abnormal specific enzymes. As researchers wondered what, precisely, was the connection between enzymes and heredity, they returned to Miescher’s discovery of nucleic acids.

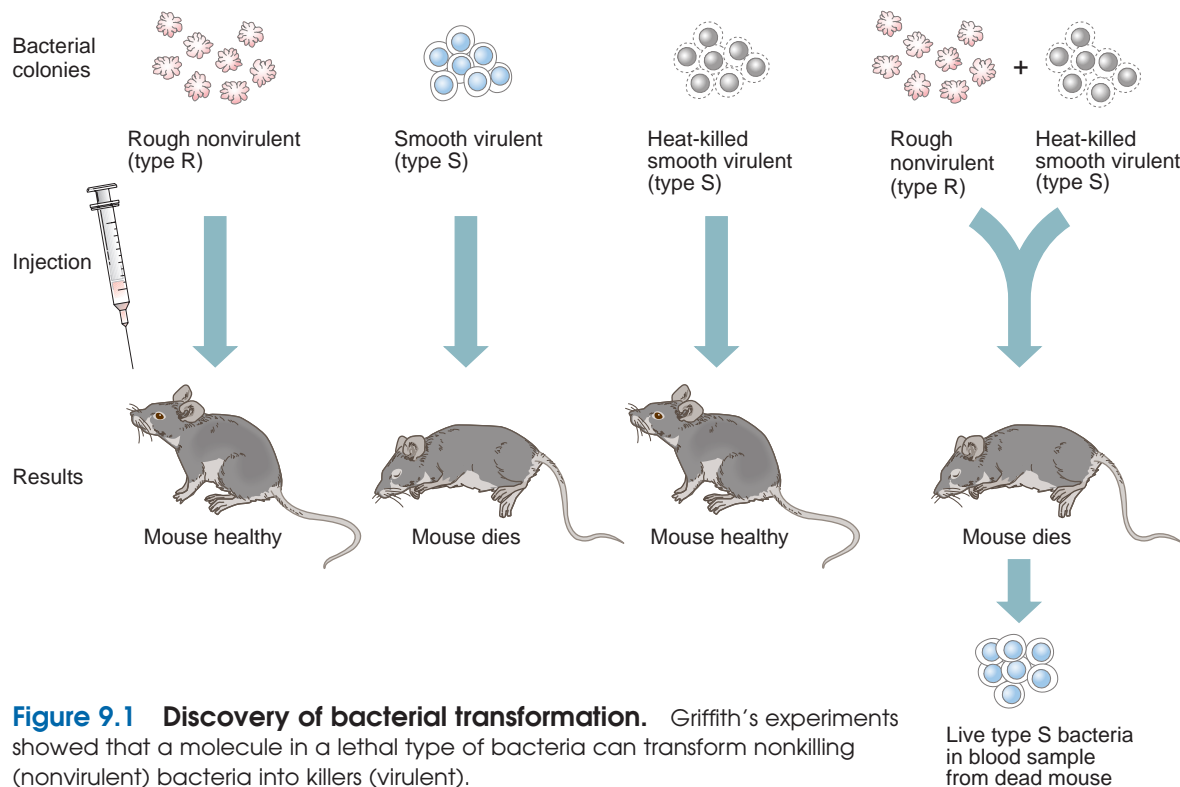
### DNA Is the Hereditary Molecule

In 1928, English microbiologist Frederick Griffith took the first step in identifying DNA as the genetic material. Griffith noticed that mice with a certain form of pneumonia harbored one of two types of *Diplococcus pneumoniae* bacteria. Type R bacteria were rough in texture. Type S bacteria were smooth because they are enclosed in a polysaccharide (a type of carbohydrate) capsule. Mice injected with type R bacteria did not develop pneumonia, but mice

injected with type S did. The polysaccharide coat shielded the bacteria from the mouse immune system, enabling them to cause severe (virulent) infection.

When type S bacteria were heated—which killed them but left their DNA intact—they no longer could cause pneumonia in mice. However, when Griffith injected mice with a mixture of type R bacteria plus heat-killed type S bacteria—neither of which, alone, was deadly to the mice—the mice died of pneumonia (**figure 9.1**). Their bodies contained live type S bacteria, encased in polysaccharide. Griffith termed the apparent conversion of one bacterial type into another “transformation.” How did it happen? What component of the dead, smooth bacteria transformed type R to type S?

U.S. physicians Oswald Avery, Colin MacLeod, and Maclyn McCarty hypothesized that a nucleic acid might be the “transforming principle.” They observed that treating broken-open type S bacteria with a protease—an enzyme that dismantles protein—did not prevent the transformation of a nonvirulent to a virulent strain, but treating it with deoxyribonuclease (or DNase), an enzyme that dismantles DNA only, did disrupt transformation. In 1944,



**Figure 9.1** Discovery of bacterial transformation. Griffith’s experiments showed that a molecule in a lethal type of bacteria can transform nonkilling (nonvirulent) bacteria into killers (virulent).

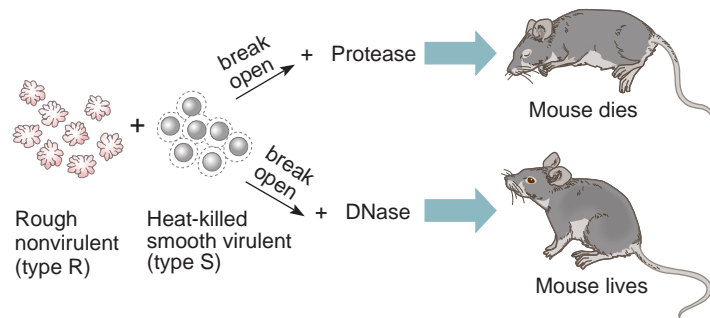
they confirmed that DNA transformed the bacteria. They isolated DNA from heat-killed type S bacteria and injected it with type R bacteria into mice (**figure 9.2**). The mice died, and their bodies contained active type S bacteria. The conclusion: DNA passed from type S bacteria into type R, enabling the type R to manufacture the smooth coat necessary for infection.

## Protein Is Not the Hereditary Molecule

Science seeks answers by eliminating explanations. To identify the genetic material, researchers also had to show that protein does *not* transmit genetic information. To do this, in 1953, U.S. microbiologists Alfred Hershey and Martha Chase used *E. coli* bacteria infected with a virus that consisted of a protein “head” surrounding DNA. Viruses infect bacterial cells by injecting their DNA (or RNA) into them. Infected bacteria may then produce many more viruses. The viral protein coats remain outside the bacterial cells.

Researchers can analyze viruses by growing them on culture medium that contains a radioactive chemical that the viruses take up. The “labeled” viral nucleic acid then emits radiation, which can be detected in several ways. When Hershey and Chase grew viruses with radioactive sulfur, the viral protein coats emitted radioactivity. When they repeated the experiment with radioactive phosphorus, the viral DNA emitted radioactivity. If protein is the genetic material, then the infected bacteria would have radioactive sulfur. But if DNA is the genetic material, then the bacteria would have radioactive phosphorus.

Hershey and Chase labeled two batches of virus, growing one in a medium containing radioactive sulfur (designated  $^{35}\text{S}$ ) and the other in a medium containing radioactive phosphorus (designated  $^{32}\text{P}$ ). The viruses grown on sulfur had their protein marked, but not their DNA, because protein incorporates sulfur but DNA does not. Conversely, the viruses grown on labeled phosphorus had their DNA marked, but not their protein, because this element is found in DNA but not protein. (Miescher had noted phosphorus in DNA from soiled bandages.)



**Figure 9.2 DNA is the “transforming principle.”** Avery, MacLeod, and McCarty identified DNA as Griffith’s transforming principle. By adding enzymes that either destroy proteins (protease) or DNA (deoxyribonuclease or DNase) to bacteria that were broken apart to release their contents, they demonstrated that DNA transforms bacteria—and that protein does not.

After allowing several minutes for the virus particles to bind to the bacteria and inject their DNA into them, Hershey and Chase agitated each mixture in a blender, shaking free the empty virus protein coats. The contents of each blender were collected in test tubes, then centrifuged (spun at high speed). This settled the bacteria at the bottom of each tube because the lighter virus coats drift down more slowly than bacteria.

At the end of the procedure, Hershey and Chase examined fractions containing the virus coats from the top of each test tube and the infected bacteria that had settled to the bottom (**figure 9.3**). In the tube containing viruses labeled with sulfur, the virus coats were radioactive, but the virus-infected bacteria, containing viral DNA, were not. In the other tube, where the virus had incorporated radioactive phosphorus, the virus coats carried no radioactive label, but the infected bacteria were radioactive. Therefore, the part of the virus that could enter bacteria and direct them to mass produce more virus was the part that had incorporated phosphorus—the DNA. The genetic material was DNA, and not protein.

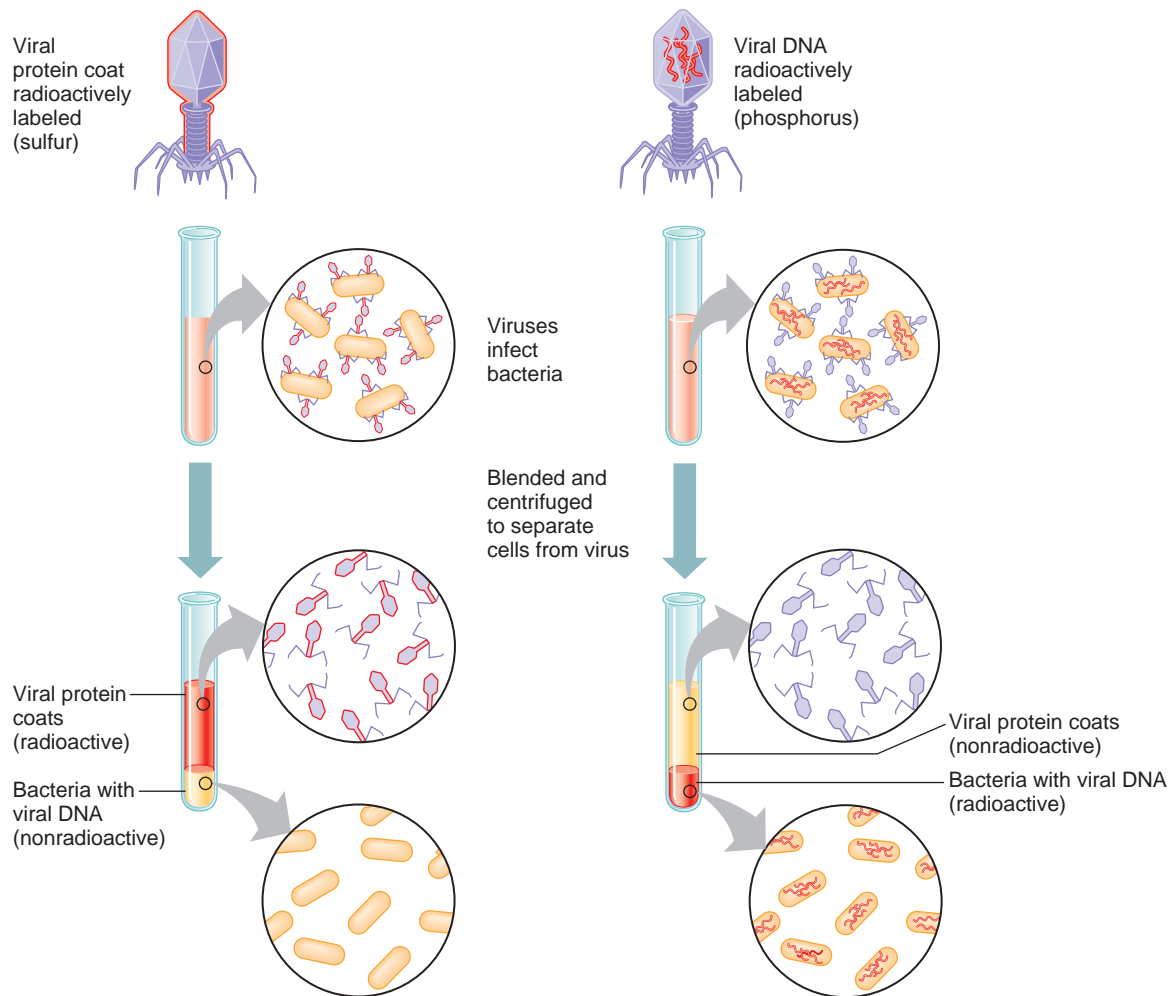
## Discovering the Structure of DNA

In 1909, Russian-American biochemist Phoebus Levene identified the 5-carbon sugar **ribose** as part of some nucleic acids, and in 1929, he discovered a similar sugar—**deoxyribose**—in other nucleic acids. He had revealed a major chemical distinction between RNA and DNA: RNA has ribose, and DNA has deoxyribose.

Levene then discovered that the three parts of a nucleic acid—a sugar, a nitrogen-containing base, and a phosphorus-containing component—are present in equal proportions. He deduced that a nucleic acid building block must contain one of each component. Furthermore, although the sugar and phosphate portions were always the same, the nitrogen-containing bases were of four types. Scientists at first thought that the bases were present in equal amounts, but if this were so, DNA could not encode as much information as it could if the number of each base type varied. Imagine how much less useful a written language would be if all the letters had to occur with equal frequency.

In the early 1950s, two lines of experimental evidence converged to provide the direct clues that finally revealed DNA’s structure. Austrian-American biochemist Erwin Chargaff showed that DNA in several species contains equal amounts of the bases **adenine** (A) and **thymine** (T) and equal amounts of the bases **guanine** (G) and **cytosine** (C). Next, English physicist Maurice Wilkins and English chemist Rosalind Franklin bombarded DNA with X rays using a technique called X-ray diffraction, then deduced information about the structure of the molecule from the patterns in which the X rays were deflected.

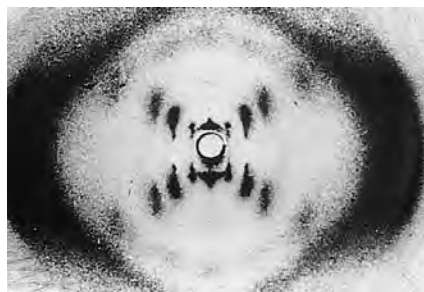
Rosalind Franklin provided a clue that would prove pivotal in revealing the structure of DNA to Watson and Crick—she distinguished two forms of DNA, a dry, crystalline “A” form, which had been well-studied, and the wetter type seen in cells, the “B” form. It took her 100 hours to obtain “photo 51”



**Figure 9.3 DNA is the hereditary material; protein is not.** Hershey and Chase used different radioactive molecules to distinguish the viral protein coat from the genetic material (DNA). These “blender experiments” showed that the virus transfers DNA, and not protein, to the bacterium. Therefore, DNA is the genetic material. The blender experiments used particular types of sulfur and phosphorus atoms that emit detectable radiation.

of the B form in May 1952 (**figure 9.4**). Its remarkable symmetry told Franklin that the molecule was a sleek helix, and revealed the position of the phosphates. She had long thought of DNA as a candidate for the genetic material. A lab notebook from her college days in 1939 bears the comment, “Geometrical basis for inheritance?” next to an illustration of a nucleic acid. By early 1953, she was very close to deducing the entire structure. On January 30, Wilkins showed Franklin’s photo 51 to Watson, who instantly recognized its importance.

The race was on. During February, famed biochemist Linus Pauling suggested a triple helix structure for DNA. Meanwhile, Watson and Crick, certain of the sugar-phosphate backbone largely from photo 51, turned their attention to the bases. Ironically, their eureka moment occurred not with



a.

**Figure 9.4 Deciphering DNA structure.** (a) Rosalind Franklin’s “photo 51” of B DNA was critical to Watson and Crick’s deduction of the three-dimensional structure of the molecule. The “X” in the center indicates a helix, and the darkened regions reveal symmetrically organized subunits. (b) Franklin died very young, of cancer. Wilkins and Crick both died in 2004.



b. Rosalind Franklin 1920-1958



sophisticated chemistry or crystallography, but while working with cardboard cutouts. On Saturday morning, February 28, Watson arrived early for a meeting with Crick. While he was waiting, he sat playing with cardboard cutouts of the four DNA bases, pairing A with A, then A with G. When he assembled A next to T, and G next to C, he noted the similar shapes, and suddenly all of the pieces fit. He had been modeling the chemical attractions between the bases that create the sleek helix.

When Crick arrived forty minutes later, the two quickly realized they had solved the puzzle of DNA's structure (figure 9.5).



**Figure 9.5 Watson and Crick.** Prints of this famed, if posed, photo fetched a high price when signed and sold at celebrations of DNA's fiftieth anniversary in 2003. Crick, told to point to the model, picked up a slide rule.

Watson, Crick, and Wilkins eventually received the Nobel prize. In 1958, Franklin died at the age of 37 from ovarian cancer, and the Nobel can only be awarded to a living person. In recent years, she has become a heroine for her role in deciphering the structure of DNA. **Table 9.1** summarizes some of the experiments that led to the discovery.

### Key Concepts

1. DNA replicates, and contains information for protein synthesis.
2. Miescher isolated DNA in 1869.
3. Garrod linked heredity to enzymes.
4. In the 1940s, Griffith identified a substance capable of transmitting infectiousness, which Avery, MacLeod, and McCarty showed was DNA.
5. Hershey and Chase confirmed that DNA, and not protein, is the genetic material.
6. Using Chargaff's discovery that the number of As equals the number of Ts, and the number of Gs equals the number of Cs, with Franklin's discovery that DNA is regular and symmetrical, Watson and Crick deciphered the structure of DNA.

## 9.2 DNA Structure

A **gene** is a section of a DNA molecule whose sequence of building blocks specifies the sequence of amino acids in a particular protein. The activity of the protein imparts the phenotype. The fact that different building blocks combine to form nucleic

acids enables them to carry information, as the letters of an alphabet combine to form words. DNA may also encode RNA that does not specify a protein, but instead assists in protein synthesis or controls gene expression. These DNA sequences are discussed in chapters 10 and 11.

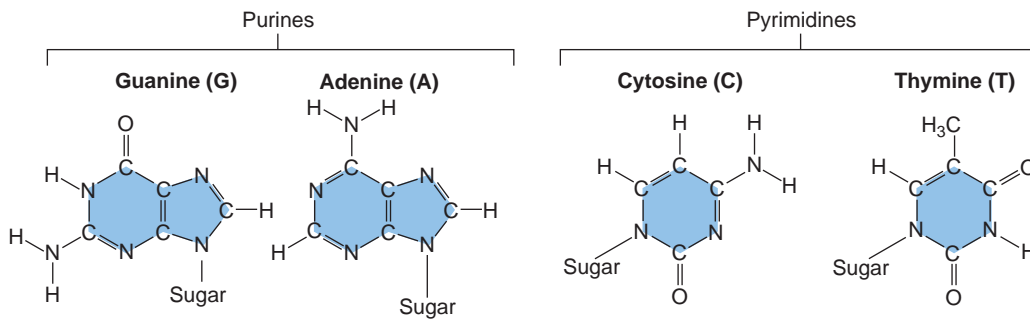
Inherited traits are diverse because proteins have diverse functions. Biological proteins are extremely varied in form and function (see table 10.1). Enzymes are responsible for pea color, plant height, and the chemical reactions of metabolism. Collagen and elastin support connective tissues, and filaments of actin and myosin slide past each other in contracting muscle. Hemoglobin transports oxygen, ferritin transports iron, and antibodies protect against infection. Malfunctioning or inactive proteins, which reflect genetic defects, can devastate health. Most of the amino acids that assemble into proteins ultimately come from the diet; the body synthesizes the others.

The structure of DNA is easiest to understand if we begin with the smallest components. A single building block of DNA is a **nucleotide**. It consists of one deoxyribose sugar, one phosphate group (a phosphorus atom bonded to four oxygen atoms), and one nitrogenous base. **Figure 9.6** shows the chemical structures of the four types of bases, and **figure 9.7** shows one of them as part of a nucleotide. Adenine (A) and guanine (G) are **purines**, which have a two-ring structure. Cytosine (C) and thymine (T) are **pyrimidines**, which have a single-ring structure. Genes or isolated pieces of DNA are measured in numbers of base pairs. A

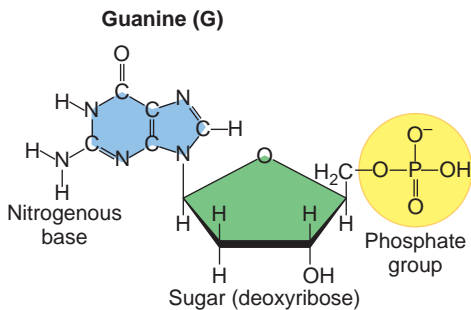
**Table 9.1**

### The Road to the Double Helix

Investigator	Contribution	Timeline
Friedrich Miescher	Isolated nuclein in white blood cell nuclei	1869
Frederick Griffith	Transferred killing ability between types of bacteria	1928
Oswald Avery, Colin MacLeod, and Maclyn McCarty	Discovered that DNA transmits killing ability in bacteria	1940s
Alfred Hershey and Martha Chase	Determined that the part of a virus that infects and replicates is its nucleic acid and not its protein	1950
Phoebus Levene, Erwin Chargaff, Maurice Wilkins, and Rosalind Franklin	Discovered DNA components, proportions, and positions	1909–early 1950s
James Watson and Francis Crick	Elucidated DNA's three-dimensional structure	1953



**Figure 9.6 DNA bases are the informational parts of nucleotides.** Adenine and guanine are purines, each composed of a six-membered organic ring plus a five-membered ring. Cytosine and thymine are pyrimidines, each with a single six-membered ring. (Within the molecules, C, H, N, O, and P are atoms of carbon, hydrogen, nitrogen, oxygen, and phosphorus, respectively.)

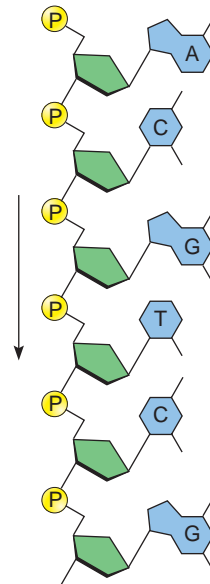


**Figure 9.7 Nucleotides.** A nucleotide of a nucleic acid consists of a 5-carbon sugar, a phosphate group, and an organic, nitrogenous base (G, A, C, or T).

particular gene, for example, may be “1,400 base pairs long.” The bases are the information-containing parts of DNA because they are the only components that can form sequences. Reading 9.1 explains how clues in DNA base sequences helped investigators solve a mystery of history.

Nucleotides join into long chains when chemical bonds form between the deoxyribose sugars and the phosphates. This creates a continuous **sugar-phosphate backbone** (figure 9.8). Two such chains of nucleotides align head-to-toe, as figure 9.9a depicts. M. C. Escher’s drawing of hands in figure 9.9b resembles the spatial relationship of the two strands of the DNA double helix.

The opposing orientation of the two nucleotide chains in a DNA molecule is called **antiparallelism**. It derives from the structure of the sugar-phosphate backbone. Antiparallelism becomes evident when the carbons of the sugars are assigned numbers to indicate their positions in the molecule

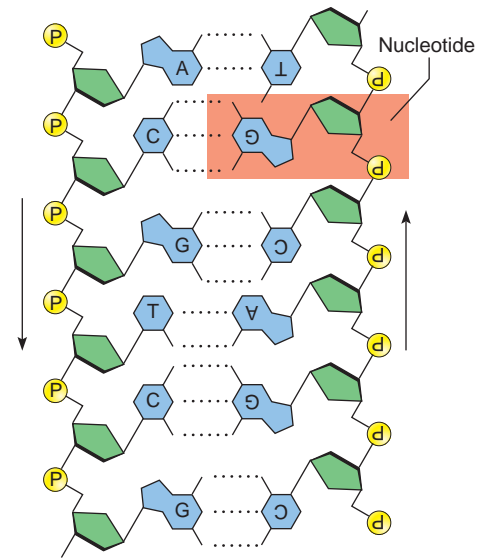


**Figure 9.8 A chain of nucleotides.**

A single DNA strand consists of a chain of nucleotides that forms when the deoxyribose sugars (green) and phosphates (yellow) bond to create a sugar-phosphate backbone. The bases A, C, G, and T are blue.

(figure 9.10). The carbons are numbered from 1 to 5, starting with the first carbon moving clockwise from the oxygen in each sugar in figure 9.11. One chain runs from the #5 carbon (top of the figure) to the #3 carbon, but the chain aligned with it runs from the #3 to the #5 carbon. These ends are depicted as “5′” and “3′”, pronounced “5 prime” and “3 prime”.

The symmetrical DNA double helix forms when nucleotides containing A pair with those containing T, and nucleotides



a.



b.

**Figure 9.9 DNA consists of two chains of nucleotides.** (a) The nitrogenous bases of one strand are held to the nitrogenous bases of the second strand by hydrogen bonds (dotted lines). Note that the sugars point in opposite directions—that is, the strands are antiparallel. (b) Artist M. C. Escher captured the essence of antiparallelism in his depiction of hands.

containing G pair with those carrying C. Because purines have two rings and pyrimidines one, the consistent pairing of a purine with a pyrimidine ensures that the double helix has the same width throughout, as Watson discovered using cardboard cutouts. These specific purine-pyrimidine couples are called **complementary base pairs**.



## Reading 9.1

### DNA Makes History

One night in July 1918, Tsar Nicholas II of Russia and his family met gruesome deaths at the hands of Bolsheviks in a Ural mountain town called Ekaterinburg (**figure 1**). Captors led the tsar, tsarina, three of their daughters, the family physician, and three servants to a cellar and shot them, bayoneting those whose diamond jewelry deflected the bullets. The executioners then stripped the bodies and loaded them onto a truck, planning to hurl them down a mine shaft. But the truck broke down, and the killers instead placed the bodies in a shallow grave, then used sulfuric acid to damage the bodies and mask their identities.

In another July—many years later, in 1991—two Russian amateur historians found the grave. Because they knew that the royal family had spent its last night in Ekaterinburg, they alerted the government that they might have unearthed the long-sought bodies of the Romanov family. An official forensic examination soon determined that the skeletons represented nine individuals. The sizes of the skeletons indicated that three were children, and the porcelain, platinum, and gold in some of the teeth suggested royalty. Unfortunately, the acid had so destroyed the facial bones that some conventional forensic tests were not feasible. But one type of evidence survived—DNA.

British researchers examined DNA from cells in the skeletal remains. DNA sequences specific to the Y chromosome distinguished males from females. Then mitochondrial DNA, inherited from mothers only, established one woman as the mother of the children. But a mother, her children, and companions were not necessarily a royal family. The researchers had to connect the skeletons to known relatives of Tsar Nicholas II. They again turned to DNA, but an inherited quirk proved, at first, to be confusing: heteroplasmy. Recall from section 5.2 that heteroplasmy exists when mitochondria in the same cell have different alleles for a gene.



**Figure 1** DNA profiling sheds light on history. DNA analysis identified the remains of the murdered Romanovs—and revealed an interesting genetic quirk.

The challenge in proving that the male remains with fancy dental work were once Tsar Nicholas II centered around nucleotide position 16169 of a mitochondrial gene whose sequence is highly variable. Some bone cells had mtDNA with cytosine (C) at this position, while some had thymine (T). Skeptics at first suspected contamination or a laboratory error, but when the odd result was repeated, researchers realized that the bone cells of this man harbored mitochondria that had *either* T or C at this position in the gene.

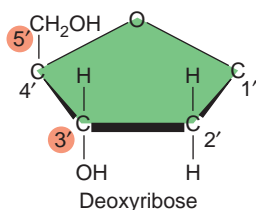
The DNA of a living blood relative of the tsar, Countess Xenia Cheremeteff-Sfiri, had only T at nucleotide site 16169. Xenia is the great-granddaughter of Tsar Nicholas II's sister. However, mitochondrial DNA from Xenia and the murdered man matched at every other site. DNA of another living relative, the Duke of Fife, the great-grandson of Nicholas's maternal aunt, matched Xenia at the famed 16169 site. A closer relative, Nicholas's nephew Tikhon Kulikovsky,

refused to lend his DNA, citing anger at the British for not assisting the tsar's family during the Bolshevik revolution.

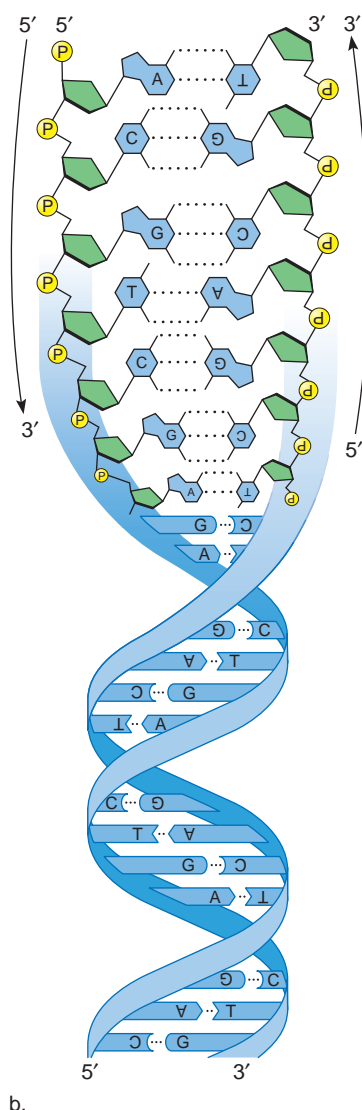
But the story wasn't over. In yet another July, in 1994, researchers would finally solve the mystery.

Attention turned to Nicholas's brother, Grand Duke of Russia Georgij Romanov. In 1899, Georgij had died at age 28 of tuberculosis. His body was exhumed in July 1994, and researchers sequenced the troublesome mitochondrial gene in bone cells from his leg. They found a match! Georgij's mitochondrial DNA had the same variable site as the man murdered in Siberia, who was, therefore, Tsar Nicholas II. The researchers calculated the probability that the remains are truly those of the tsar, rather than resembling Georgij's unusual DNA sequence by chance, as 130 million to 1. At least part of the murdered Russian royal family can finally rest in peace, thanks to DNA analysis. The bodies of the two youngest children, Alexis and Anastasia, were not found.





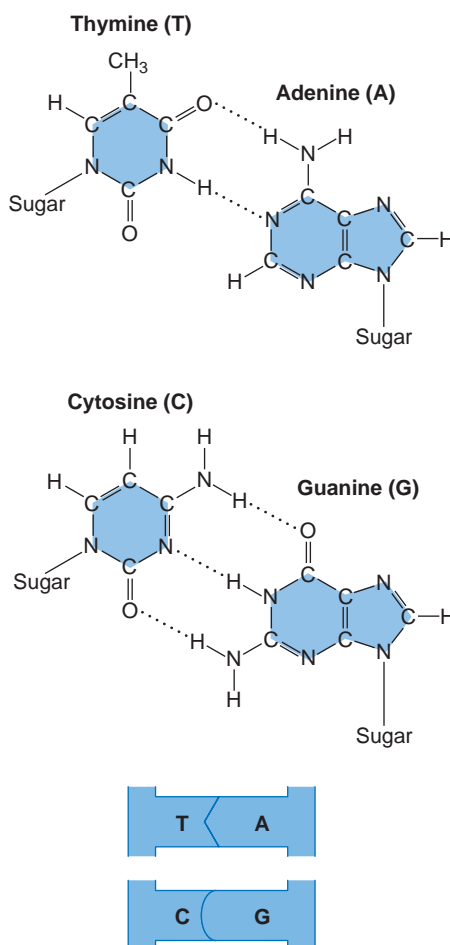
**Figure 9.10 Antiparallelism.** The antiparallel nature of the DNA double helix becomes apparent when the carbons in the sugar are numbered.



**Figure 9.11 DNA is directional.** Antiparallelism in a DNA molecule arises from the orientation of the deoxyribose sugars. One-half of the double helix runs in a 5' to 3' direction, and the other half runs in a 3' to 5' direction.

Chemical attractions called hydrogen bonds hold the base pairs together. Two hydrogen bonds join A and T, and three hydrogen bonds join G and C, as **figure 9.12** shows. Finally, DNA forms a double helix when the antiparallel, base-paired strands twist about one another in a regular fashion. The double-stranded, helical structure of DNA gives it great strength—50 times the strength of single-stranded DNA, which would not form a helix.

DNA molecules are incredibly long. The DNA of the smallest human chromosome, if stretched out, would be 14 millimeters long. But it is packed into a chromosome that, during cell division, is only 2 micrometers long. This means that the DNA



**Figure 9.12 DNA base pairs.** The key to the constant width of the DNA double helix is the pairing of purines with pyrimidines. Two hydrogen bonds join adenine and thymine; three hydrogen bonds link cytosine and guanine.

molecule must fold so tightly that its compacted length shrinks by a factor of 7,000:

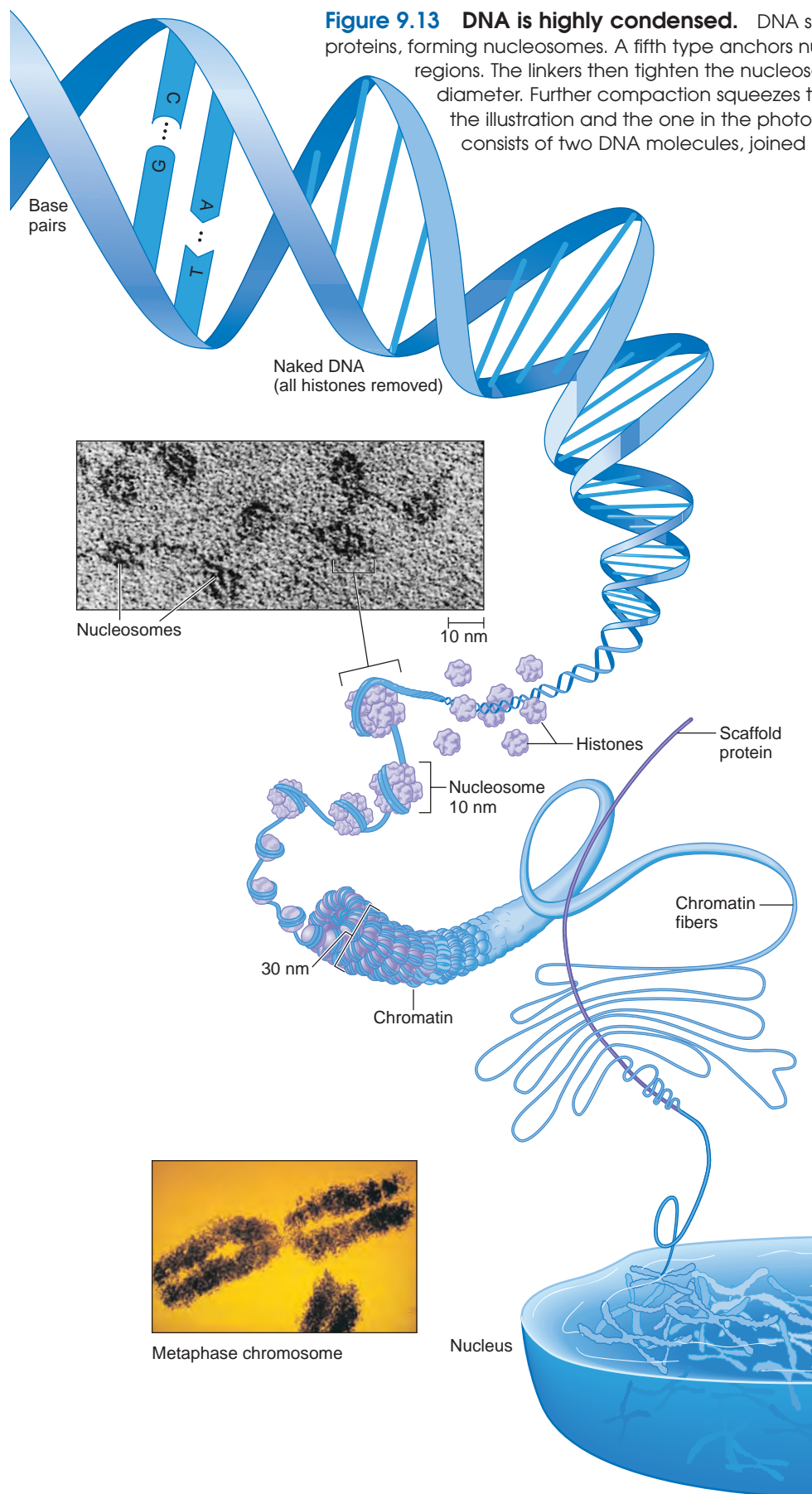
$$\left( \frac{14 \times 10^{-3} \text{ meters}}{2 \times 10^{-6} \text{ meters}} \right)$$

Various types of proteins compress the DNA without damaging or tangling it. Scaffold proteins form frameworks that guide DNA strands. Then, the DNA coils around proteins called **histones**, forming a beads-on-a-string-like structure. The bead part is called a **nucleosome**. It is a little like wrapping a very long, thin piece of thread around your fingers, to keep it from unraveling and tangling. DNA wraps at several levels, until it is compacted into a chromosome (**figure 9.13**). Specifically, a nucleosome forms around packets of eight histone proteins (a pair of each of four types). A fifth type anchors nucleosomes to short “linker” regions of DNA, which then tighten the nucleosomes into fibers 30 nanometers (nm) in diameter. As a result, at any given time, only small portions of the DNA double helix are exposed. Chemical modification of the histones controls when particular DNA sequences are accessible. (This is discussed further in chapter 11.) DNA also unwinds locally when it replicates.

Altogether, the chromosome substance is called **chromatin**, which means “colored material.” Chromatin is not just DNA; it is about 30 percent histone proteins, 30 percent DNA binding proteins, 30 percent DNA, and 10 percent RNA. Points along the chromatin attach it, in great loops, to the inner face of the nuclear membrane. Without the proteins that are part of chromatin, it is unlikely that DNA would be biologically useful.

## Key Concepts

1. The DNA double helix's backbone is alternating deoxyribose and phosphate held together by complementary pairs of A-T and G-C bases. A and G are purines; T and C are pyrimidines.
2. The DNA double helix is antiparallel, its strands running in an opposite head-to-toe manner.
3. DNA winds tightly about histone proteins, forming nucleosomes, which in turn wind tighter, forming chromatin.



**Figure 9.13 DNA is highly condensed.** DNA spools around octets of four types of histone proteins, forming nucleosomes. A fifth type anchors nucleosomes to connecting short “linker” regions. The linkers then tighten the nucleosomes into fibers 30 nanometers (nm) in diameter. Further compaction squeezes the DNA into the nucleus. The chromosomes in the illustration and the one in the photograph are in the replicated form. That is, each consists of two DNA molecules, joined at the centromere.

## 9.3 DNA Replication—Maintaining Genetic Information

As soon as Watson and Crick deciphered the structure of DNA, its mechanism for replication became obvious. They ended their report on the structure of DNA with the statement, *It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.*

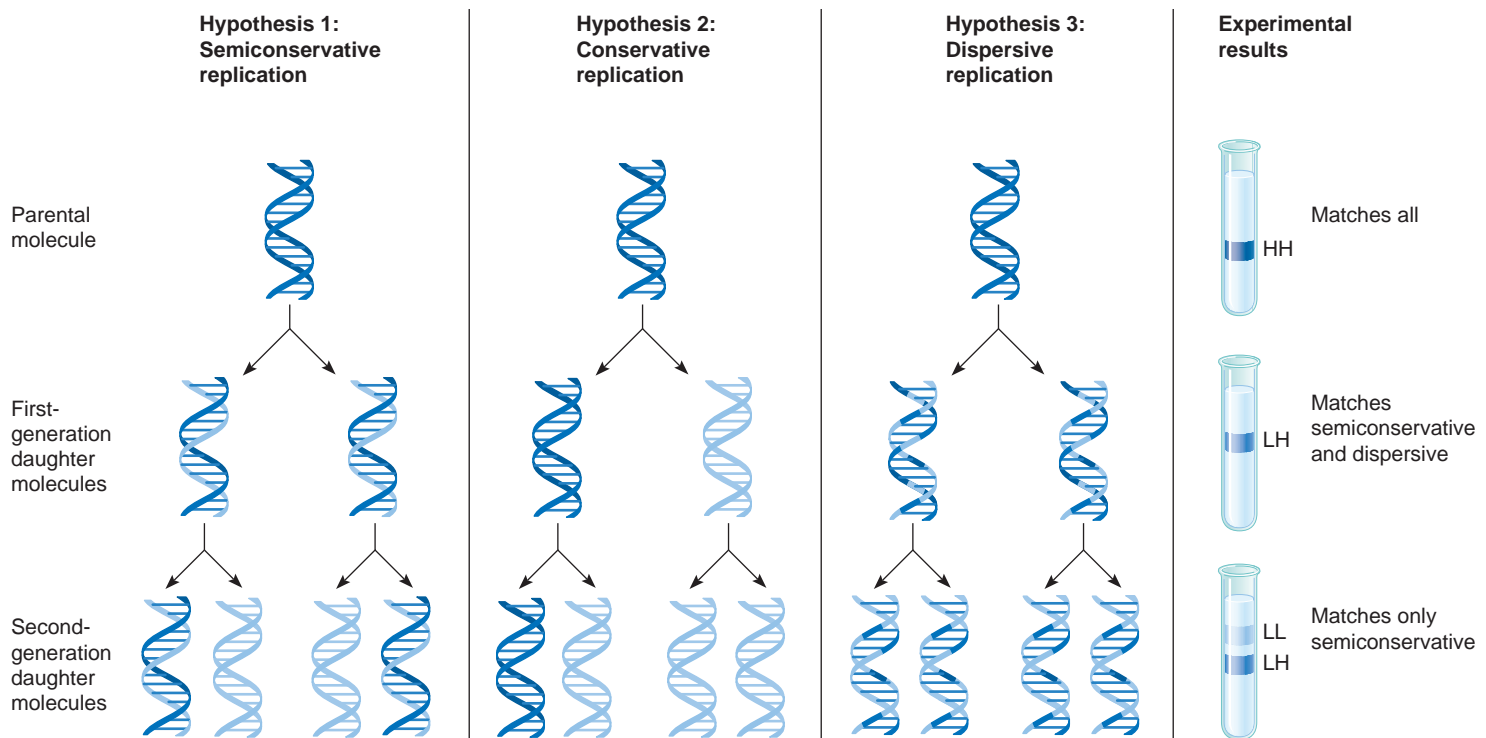
Thirty years after Watson and Crick’s discovery, biochemist Kary Mullis invented a way to harness DNA replication to mass-produce selected DNA sequences in the laboratory. His polymerase chain reaction (PCR) revolutionized biology research and inspired several other types of DNA amplification technologies. PCR is discussed in section 19.2.

### Replication Is Semiconservative

Watson and Crick envisioned the two halves of the DNA double helix unwinding and separating, exposing unpaired bases that would attract their complements. Two double helices would thus form from one. This route to replication is called **semiconservative**, because each new DNA double helix conserves half of the original. But separating the long strands posed a huge physical challenge, a little like having to keep two pieces of thread the length of a football field from tangling!

Some researchers suggested that DNA might replicate in any of three possible ways: semiconservative; conservative, with one double helix specifying creation of a second double helix; or dispersive, with a double helix shattering into pieces that would join with newly synthesized DNA pieces to form two molecules (**figure 9.14**).

An experimental approach to reveal how DNA replicates was first suggested in 1941,



**Figure 9.14 Three models for DNA replication.** Density shift experiments distinguished the three hypothesized mechanisms of DNA replication. DNA molecules containing light nitrogen are designated “LL” and those with heavy nitrogen, “HH.” Molecules containing both isotopes are designated “LH.” These experiments established that DNA replication is semiconservative. The first three columns illustrate how parental and daughter DNA would be distributed in each of the three mechanisms of DNA replication. The fourth column depicts the density of the DNA at each stage for each of the three hypothesized replication mechanisms.

when English geneticist J. B. S. Haldane wrote, *How can one distinguish between model and copy? Perhaps you could use heavy nitrogen atoms in the food supplied to your cell, hoping that the “copy” genes would contain it while the models did not.*

In 1957, two young researchers, Matthew Meselson and Franklin Stahl, tried Haldane’s experiment using bacteria. Their experiments beautifully illustrated scientific inquiry, because their evidence not only supported one hypothesis (semiconservative replication), but disproved the other two (conservative replication and dispersive replication).

Meselson and Stahl labeled DNA newly synthesized by bacteria with heavy nitrogen ( $^{15}\text{N}$ ) in the media. The DNA could then be distinguished from older DNA that had been synthesized with the more common lighter form,  $^{14}\text{N}$ . The idea was that DNA that incorporated the heavy nitrogen could be separated from newly synthesized DNA that incorporated the normal lighter nitrogen by its greater density. DNA in which one-half of the double helix was light and

one-half heavy would be of intermediate density.

In their density shift experiments, Meselson and Stahl grew cells on media with heavy nitrogen and then shifted the cells to media with light nitrogen. They traced replicating DNA through several cell divisions. The researchers grew cells, broke them open, extracted DNA, and spun it in a centrifuge. The heavier DNA sank to the bottom of the centrifuge tube, the light DNA rose to the top, and the heavy-light double helices settled in the middle area of the tube.

Meselson and Stahl grew *E. coli* on media containing  $^{15}\text{N}$  for several generations, making all of the DNA heavy. They knew this because only “heavy-heavy” molecules appeared in the tube after centrifugation. They then shifted the bacteria to media containing  $^{14}\text{N}$ , allowing enough time for the bacteria to divide only once (about 30 minutes).

When Meselson and Stahl collected the DNA after one generation and centrifuged it, the double helices were all of intermediate density. The DNA settled in the middle

of the tube, indicating that the molecules contained half  $^{14}\text{N}$  and half  $^{15}\text{N}$ . This pattern was consistent with either semiconservative DNA replication or a dispersive mechanism. In contrast, the result of conservative replication would have been one band of material in the tube completely labeled with  $^{15}\text{N}$ , corresponding to one double helix, and another totally “light” band containing  $^{14}\text{N}$  only, corresponding to the other double helix. This did not happen. Conservative replication as an explanation could be eliminated.

To definitively distinguish among the three routes to DNA replication, Meselson and Stahl extended the experiment one more generation. If the semiconservative mechanism held up, each hybrid (half  $^{14}\text{N}$  and half  $^{15}\text{N}$ ) double helix present after the first generation following the shift to  $^{14}\text{N}$  medium would separate and assemble a new half from bases labeled only with  $^{14}\text{N}$ . This would produce two double helices with one  $^{15}\text{N}$  (heavy) and one  $^{14}\text{N}$  (light) chain, plus two double helices containing only  $^{14}\text{N}$ . The tube would have one heavy-light band and



one light-light band. This is indeed what Meselson and Stahl saw.

The conservative mechanism would have yielded two bands in the tube in the third generation, indicating three completely light double helices for every completely heavy one, as the bottom portion of the hypothesis 2 column indicates in figure 9.14. The third generation for the dispersive model would have been a single large band, somewhat higher than the second-generation band because additional  $^{14}\text{N}$  would have been randomly incorporated into the DNA.

After experiments demonstrated the semiconservative nature of DNA replication, the next challenge was to decipher the steps of the process.

## Steps of DNA Replication

DNA replication occurs during S phase of the cell cycle (see figure 2.13). When DNA replicates, it unwinds, breaks, builds a new nucleotide chain, and mends (figure 9.15). Enzymes called helicases unwind and hold

apart replicating DNA, enabling other enzymes to guide the assembly of a new DNA strand.

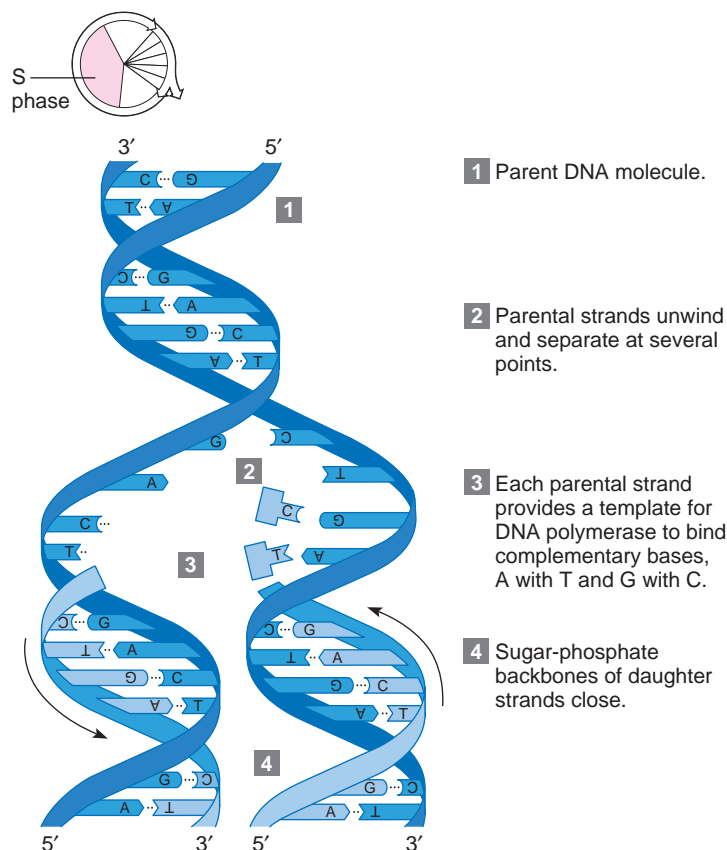
Human DNA replicates about 50 bases per second. To get the job done, a human chromosome replicates simultaneously at hundreds of points along its length, and the pieces join. A site where DNA is locally opened, resembling a fork, is called a **replication fork**.

DNA replication begins when a helicase breaks the hydrogen bonds that connect a base pair (figure 9.16). Binding proteins hold the two strands apart. Another enzyme, primase, then attracts complementary RNA nucleotides to build a short piece of RNA, called an RNA primer, at the start of each segment of DNA to be replicated. The RNA primer is required because the major replication enzyme, **DNA polymerase** (DNAP), can only add bases to an existing nucleic acid strand. (A polymerase is an enzyme that builds a polymer, which is a chain of chemical building blocks.) Next, the RNA primer attracts DNAP, which

brings in DNA nucleotides complementary to the exposed bases on the parental strand; this strand serves as a mold, or template. New bases are added one at a time, starting at the RNA primer. The new DNA strand grows as hydrogen bonds form between the complementary bases. The nucleotides are abundant in cells, and are synthesized from dietary nutrients.

DNAP works directionally, adding new nucleotides to the exposed 3' end of the sugar in the growing strand. Overall, replication proceeds in a 5' to 3' direction, because this is the only chemical configuration in which DNAP can add bases. How can the growing fork proceed in one direction, when both parental strands must be replicated? The answer is that on at least one strand, replication is discontinuous. It is accomplished in small pieces from the inner part of the fork outward, in a pattern similar to backstitching. **Ligase** is an enzyme that then seals the sugar-phosphate backbones of the pieces, building the new strand. These pieces, up to 150 nucleotides long, are called Okazaki fragments, after their discoverer (see figure 9.16).

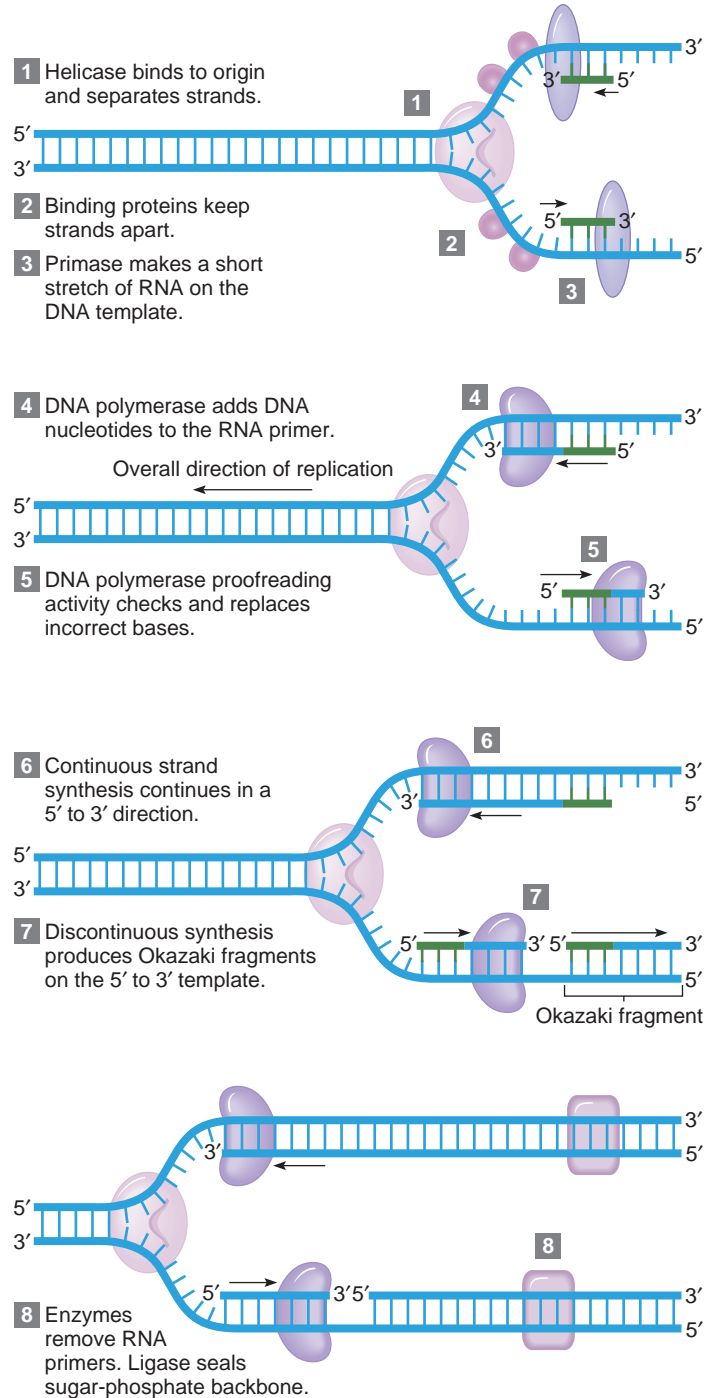
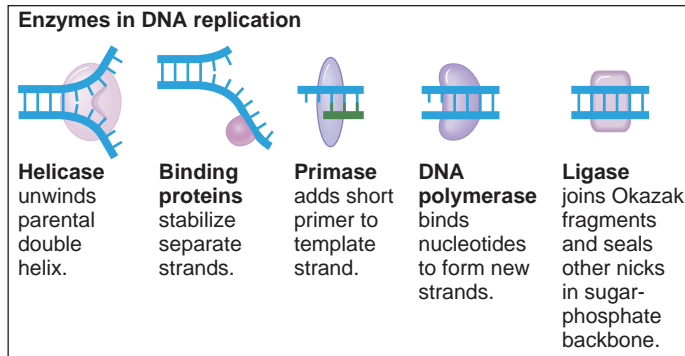
DNA polymerase also “proofreads” as it goes, excising mismatched bases and inserting correct ones. It also removes the RNA primer and replaces it with the correct DNA bases. Finally, ligases seal the entire sugar-phosphate backbone. Ligase comes from a Latin word meaning “to tie.”



**Figure 9.15** Overview of DNA replication.

## Key Concepts

1. Experiments that followed the distribution of labeled DNA showed that DNA replication is semiconservative, not conservative or dispersive.
2. Enzymes replicate DNA.
3. DNA replication occurs simultaneously at several points on each chromosome, and the pieces join.
4. At each initiation site, primase directs synthesis of a short RNA primer, which DNA eventually replaces. DNA polymerase adds complementary bases to the RNA primer. Ligase joins the sugar-phosphate backbone.
5. DNA is synthesized in a 5' to 3' direction, discontinuously on one strand.



**Figure 9.16 Activities at the replication fork.** DNA replication takes many steps.

# Summary

## 9.1 Experiments Identify and Describe the Genetic Material

1. DNA encodes information that the cell uses to synthesize protein. DNA can also replicate, passing on its information.
2. Many experimenters described DNA as the hereditary material. Miescher identified DNA in white blood cell nuclei. Garrod connected heredity to enzyme abnormalities. Griffith identified a “transforming principle” that transmitted infectiousness in pneumonia-causing bacteria; Avery, MacLeod, and McCarty discovered that the transforming principle is DNA; and Hershey and Chase confirmed that the genetic material is DNA and not protein.
3. Levene described the three components of a DNA building block and found that they

appear in DNA in equal amounts. Chargaff discovered that the amount of **adenine** (A) equals the amount of **thymine** (T), and the amount of **guanine** (G) equals that of **cytosine** (C). A and G are **purines**; C and T are **pyrimidines**. Rosalind Franklin showed that the molecule is a certain type of helix. Watson and Crick deduced DNA’s structure.

## 9.2 DNA Structure

4. A **nucleotide** is a DNA building block. It consists of a **deoxyribose**, a phosphate, and a nitrogenous base.
5. The rungs of the DNA double helix consist of hydrogen-bonded **complementary base pairs** (A with T, and C with G). The rails are chains of alternating sugars and phosphates that run **antiparallel** to each

other. DNA is highly coiled, and complexed with protein to form **chromatin**.

## 9.3 DNA Replication—Maintaining Genetic Information

6. Meselson and Stahl demonstrated the **semiconservative** nature of DNA replication with density shift experiments.
7. During replication, the DNA unwinds locally at several sites. **Replication forks** form as hydrogen bonds break between base pairs. Primase builds short RNA primers, which DNA sequences eventually replace. Next, **DNA polymerase** fills in DNA bases, and **ligase** seals the sugar-phosphate backbone.
8. Replication proceeds in a 5′ to 3′ direction, so the process must be discontinuous in short stretches on one strand.

# Review Questions

1. List the components of a nucleotide.
2. How does a purine differ from a pyrimidine?
3. DNA specifies and regulates the cell’s synthesis of protein. If a cell contains all the genetic material required to carry out protein synthesis, why must its DNA be replicated?
4. Why would a DNA structure in which each base type could form hydrogen bonds with any of the other three base types not produce a molecule that is easily replicated?
5. What part of the DNA molecule encodes information?
6. Explain how DNA is a directional molecule in a chemical sense.
7. Match the experiment described in the left column to a concept it illustrates in the right column (more than one answer may be possible).

1. Density shift experiments	a. DNA is the hereditary material
2. Discovery of an acidic substance that includes nitrogen and phosphorus on dirty bandages	b. Complementary base pairing is part of DNA structure and maintains a symmetrical double helix
3. “Blender experiments” that showed that the part of a virus that infects bacteria contains phosphorus, but not sulfur	c. Identification of nuclein
4. Determination that DNA contains equal amounts of guanine and cytosine, and of adenine and thymine	d. DNA, not protein, is the hereditary material
5. Discovery that bacteria can transfer a “factor” that transforms a harmless strain into a lethal one	e. DNA replication is semiconservative, not conservative or dispersive
8. Place the following enzymes in the order in which they begin to function in DNA replication.

ligase	primase
exonuclease	helicase
DNA polymerase	
9. How can incredibly long DNA molecules fit into a cell’s nucleus?
10. Place in increasing size order:

nucleosome
histone protein
chromatin
11. How are very long strands of DNA replicated without twisting into a huge tangle?
12. List the steps in DNA replication.
13. Why must DNA be replicated continuously as well as discontinuously?
14. How does RNA participate in DNA replication?
15. Describe two experiments that supported one hypothesis while also disproving another.



# Applied Questions

1. In Bloom syndrome, ligase malfunctions. As a result, replication forks move too slowly. Why?
2. DNA contains the information that a cell uses to synthesize a particular protein. How do proteins assist in DNA replication?
3. A person with deficient or abnormal ligase may have an increased cancer risk and chromosome breaks that cannot heal. The person is, nevertheless, alive. Why are there no people who lack DNA polymerase?
4. Write the sequence of a strand of DNA replicated from each of the following base sequences:
  - a. T C G A G A A T C T C G A T T
  - b. C C G T A T A G C C G G T A C
  - c. A T C G G A T C G C T A C T G
5. Which do you think was the more far-reaching accomplishment, determining the structure of DNA, or sequencing the human genome? State a reason for your answer.

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 9** and **Web Activities** to find the website links needed to complete the following activities.

6. The Frozen Ark project is an international consortium of zoos, laboratories, and museums that is preserving DNA samples from endangered animal species. Consult <http://www.frozenark.org>
  - a. Follow one of the links and describe an endangered species. What do you think is the value of this project?
  - b. Do you think the project should be extended to include organisms other than animals? Cite a reason for your answer.
  - c. What would be the difficulties encountered in attempting to increase population sizes of endangered species using stored DNA?
7. Visit the Cystic Fibrosis Mutation Database website. Select twenty contiguous bases of

the sequence for the cystic fibrosis gene and write the complementary sequence.

## Case Studies and Research Results

8. A very expensive diamond necklace was ripped off the neck of a celebrity who had borrowed it to wear for the opening of her new film. She noticed the crime right away, but the robber had already escaped. Unfortunately for him, he had a cold, and had dribbled a few drops of nasal secretion onto the back of the celebrity's neck—which a nearby police officer had the presence of mind to sample. In it were cells from the perpetrator's nose lining. Analysis of mitochondrial DNA, however, revealed two different DNA sequences. Detective Stabler concluded that there were two robbers, but the celebrity insisted that she had seen only one man run away. What is another explanation for finding two types of mitochondrial DNA?

# A Second Look

1. Describe a recent news event, feature article, film, or television program that mentions a DNA sequence.
2. Cite an example of how knowing a DNA sequence could be abused.
3. Provide an example of how knowing a DNA sequence could be helpful.
4. People often use the phrase “the gene for” to describe traits that do not necessarily or directly arise from a protein's actions, such as “a gene for jealousy” or “a gene for acting.” How would you explain to them what a gene actually is?

Learn to apply the skills of a genetic counselor with this additional case found in the *Case Workbook in Human Genetics*:

DNA replication



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Gene Action: From DNA to Protein

## CHAPTER CONTENTS

### 10.1 Transcription

- RNA Structure and Types
- Transcription Factors
- Steps of Transcription
- RNA Processing

### 10.2 Translation of a Protein

- Deciphering the Genetic Code
- Building a Protein
- Solving a Problem: From DNA to RNA to Protein

### 10.3 Protein Folding

## THE EVOLVING STORY OF MARFAN SYNDROME

In most people with Marfan syndrome, lack of a protein that binds the elastic fibers of connective tissue, called fibrillin, weakens heart valves and the wall of the aorta (the body's largest artery) and dislocates the lenses of the eyes. But the inheritance of Marfan syndrome was confusing. Some people also have long limbs and emphysema, and rarely people with Marfan syndrome symptoms do not have mutations in the fibrillin gene. Mice that have Marfan syndrome *all* have emphysema as well as the heart defects. Researchers learned from studying the mice that the tiny air sacs (alveoli) that disintegrate in smoking-induced emphysema in people simply never form in the mice.

To solve the mystery, investigators searched DNA sequence databases to identify genes that fibrillin resembles or interacts with—this might provide a clue to something that fibrillin does besides bind elastic fibers. Indeed, the fibrillin gene is very similar to a gene that encodes a protein that binds a growth factor, called transforming growth factor beta (TGF- $\beta$ ). Might fibrillin also bind TGF- $\beta$ ?

Experiments with mice revealed that fibrillin normally binds TGF- $\beta$ . When fibrillin is lacking, free TGF- $\beta$  builds up—which causes the unexplained symptoms. The few individuals with the disease who have normal fibrillin genes instead have mutations in TGF-B. This new view of Marfan syndrome may lead to a treatment. A drug used to treat kidney failure, Losartan, blocks TGF- $\beta$ . Given to Marfan mice, the drug treats the emphysema and heart problems. Clinical trials are ongoing for children with Marfan syndrome.



In 1961, a doctor diagnosed Abraham Lincoln with Marfan syndrome based on phenotype. It will take genetic tests—of two genes—to determine whether or not he really had this inherited disease.

DNA replication preserves genetic information by giving each new cell a complete set of operating instructions. A cell uses some of the information to manufacture proteins, which have a great variety of functions (**table 10.1**).

A protein consists of one or more long chains of amino acids called polypeptides. A short sequence of amino acids is called a peptide, and the bonds that join amino acids are called peptide bonds.

To use the genetic information in the nucleus, the process of **transcription** first copies a gene into an RNA molecule that is complementary to one strand of the DNA double helix. The copy is taken out of the nucleus and into the cytoplasm. There, the process of **translation** uses the information in three types of RNA to manufacture a protein by aligning and joining specified amino acids. Finally, the protein must fold into a specific three-dimensional form in order to function.

Cells replicate their DNA only during S phase of the cell cycle. In contrast, transcription and translation occur continuously, except during M phase. Transcription and translation supply the proteins essential for life, as well as those that give a cell its specialized characteristics. This chapter considers the steps of transcription and translation, and chapter 11 discusses control of these processes.

### 10.1 Transcription

Watson and Crick, shortly after publishing their structure of DNA in 1953, described the relationship between nucleic acids and proteins as a directional flow of information called the “central dogma” (**figure 10.1**). As Francis Crick explained in 1957, “*The specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and this sequence is a code for the amino acid sequence of a particular protein.*” This statement inspired more than a decade of intense research to identify the participants in protein synthesis and discover how they interact. At center stage: RNA.

RNA is the bridge between gene and protein. RNA and DNA share an intimate

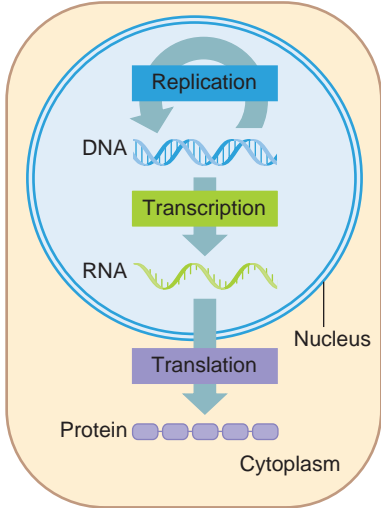
**Table 10.1**  
Protein Diversity in the Human Body

Protein	Function
Actin, myosin, dystrophin	Muscle contraction
Antibodies, antigens, cytokines	Immunity
Carbohydrases, lipases, proteases, nucleases	Digestion (digestive enzymes)
Casein	Milk protein
Collagen, elastin, fibrillin	Connective tissue
Colony-stimulating factors, erythropoietin	Blood cell formation
DNA and RNA polymerase	DNA replication, gene expression
Ferritin	Iron transport in blood
Fibrin, thrombin	Blood clotting
Growth factors, kinases, cyclins	Cell division
Hemoglobin, myoglobin	Oxygen transport
Insulin, glucagon	Control of blood glucose level
Keratin	Hair structure
Tubulin, actin	Cell movements
Tumor suppressors	Cancer prevention

relationship, as **figure 10.2** depicts. RNA is synthesized against (is complementary to) one strand of the double helix, called the **template strand**, with the assistance of an enzyme, **RNA polymerase**. The other strand of the DNA double helix is called the **coding strand**.

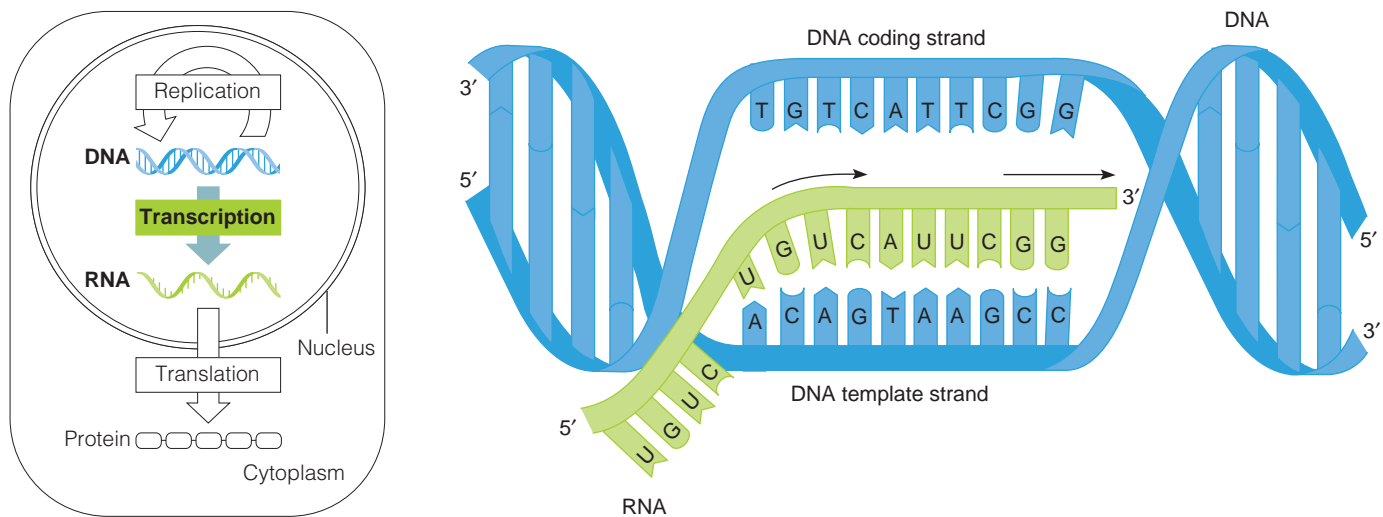
### RNA Structure and Types

RNA and DNA have similarities and differences (**figure 10.3** and **table 10.2**). Both are nucleic acids, consisting of sequences of nitrogen-containing bases joined by sugar-phosphate backbones. However, RNA is usually single-stranded, whereas DNA is double-stranded. Also, RNA has the pyrimidine base **uracil** where DNA has thymine. As their names imply, RNA nucleotides include the sugar ribose, rather than DNA’s deoxyribose. Functionally, DNA stores genetic information, whereas RNA controls how that information is used.

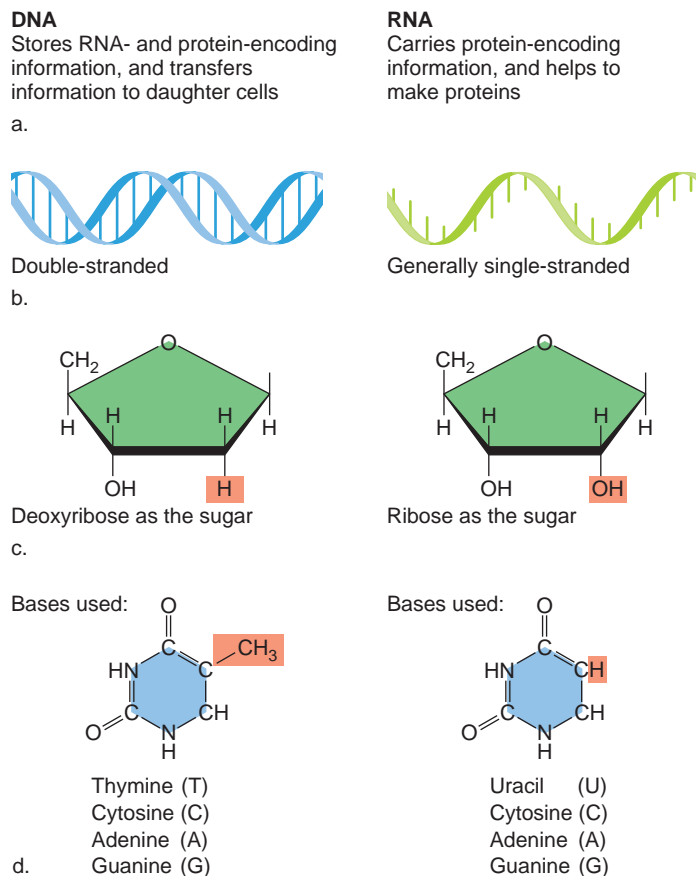


**Figure 10.1** DNA to RNA to protein. The central dogma of molecular biology states that information stored in DNA is copied to RNA (transcription), which is used to assemble proteins (translation). DNA replication perpetuates genetic information. This figure repeats within the chapter, with the part under discussion highlighted.





**Figure 10.2** The relationship among RNA, the DNA template strand, and the DNA coding strand. The RNA sequence is complementary to the DNA template strand. This is the same sequence as the DNA coding strand, with uracil (U) in place of thymine (T).



**Figure 10.3** DNA and RNA differences. (a) DNA is double-stranded; RNA is usually single-stranded (b). DNA nucleotides include deoxyribose, whereas RNA nucleotides have ribose (c). Finally, DNA nucleotides include the pyrimidine thymine, whereas RNA has uracil (d).

As RNA is synthesized along DNA, it folds into a three-dimensional shape, or **conformation**, that is determined by complementary base pairing within the same RNA molecule. For example, a sequence of AAUUUCC might hydrogen bond to a sequence of UUAAGG—its complement—elsewhere in the same molecule. These shapes are very important for RNA's functioning. The three major types of RNA are messenger RNA, ribosomal RNA, and transfer RNA (**table 10.3**). Table 11.4 describes other types of RNA molecules.

**Messenger RNA (mRNA)** carries the information that specifies a particular protein. Each three mRNA bases in a row form a genetic code word, or **codon**, that specifies a certain amino acid. Because genes vary in length, so do mature mRNA molecules. Most mRNAs are 500 to 4,500 bases long. Differentiated cells can carry out specialized functions because they “express” certain subsets of genes—that is, they produce certain mRNA molecules, or transcripts. The information in the transcripts is then used to manufacture the encoded proteins. A muscle cell, for example, has many mRNAs that specify the contractile proteins actin and myosin, whereas a skin cell contains many mRNAs that specify the scaly keratin proteins.

Table 10.2

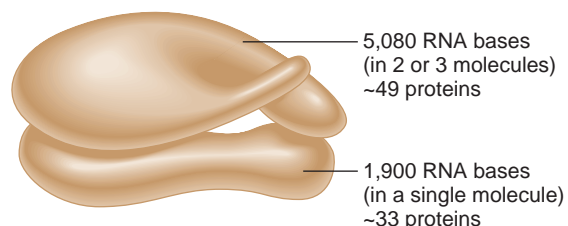
## How DNA and RNA Differ

DNA	RNA
1. Usually double-stranded	1. Usually single-stranded
2. Thymine as a base	2. Uracil as a base
3. Deoxyribose as the sugar	3. Ribose as the sugar
4. Maintains protein-encoding information	4. Carries protein-encoding information and controls how information is used
5. Cannot function as an enzyme	5. Can function as an enzyme

Table 10.3

## Major Types of RNA

Type of RNA	Size (number of nucleotides)	Function
mRNA	500–4,500+	Encodes amino acid sequence
rRNA	100–3,000	Associates with proteins to form ribosomes, which structurally support and catalyze protein synthesis
tRNA	75–80	Transports specific amino acids to the ribosome for protein synthesis



**Figure 10.4 The ribosome.** A ribosome from a eukaryotic cell has two subunits; together, they consist of 82 proteins and four rRNA molecules.

To use the information in an mRNA sequence, a cell requires two other major classes of RNA. **Ribosomal RNA (rRNA)** molecules range from 100 to nearly 3,000 nucleotides long. Ribosomal RNAs associate with certain proteins to form a ribosome. Recall from chapter 2 that a ribosome is a structural support for protein synthesis (figure 10.4).

A ribosome has two subunits that are separate in the cytoplasm but join at the site of initiation of protein synthesis. The larger ribosomal subunit has three types of rRNA molecules, and the small subunit

has one. Ribosomal RNA, however, is more than a structural support. Certain rRNAs catalyze the formation of the peptide bonds between amino acids. Such an RNA with enzymatic function is called a ribozyme. Other rRNAs help to align the ribosome and mRNA.

The third major type of RNA molecule, **transfer RNA (tRNA)**, binds an mRNA codon at one end and a specific amino acid at the other. A tRNA molecule is only 75 to 80 nucleotides long. Some of its bases weakly bond with each other, folding the tRNA into loops in a characteristic

cloverleaf shape (figure 10.5). One loop of the tRNA has three bases in a row that form the **anticodon**, which is complementary to an mRNA codon. The end of the tRNA opposite the anticodon strongly bonds to a specific amino acid. A tRNA with a particular anticodon sequence always carries the same amino acid. (Organisms have 20 types of amino acids.) For example, a tRNA with the anticodon sequence GAA always picks up the amino acid phenylalanine. Enzymes attach amino acids to tRNAs that bear the appropriate anticodons (figure 10.6).

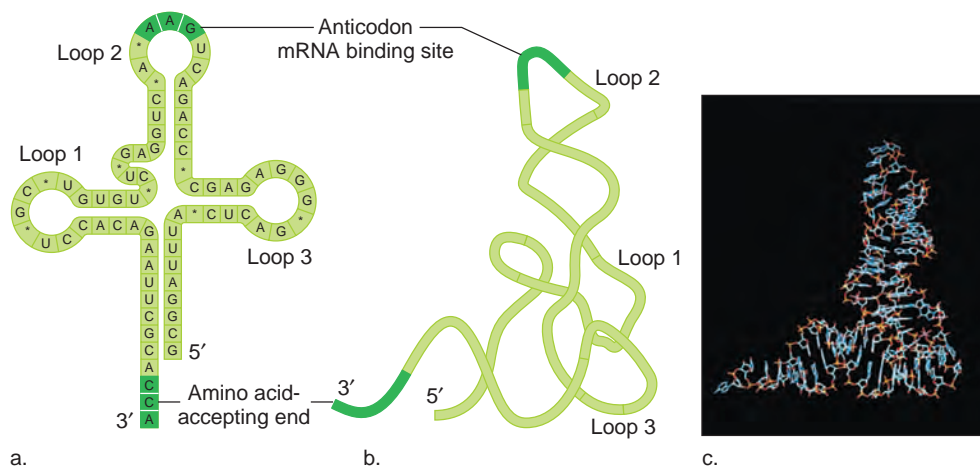
## Transcription Factors

Study of the control of gene expression began in 1961, when French biologists François Jacob and Jacques Monod described the remarkable ability of *E. coli* bacteria to produce the enzymes to metabolize the sugar lactose—but only when lactose is in the cell’s surroundings. What “tells” a simple bacterial cell to transcribe the proteins it needs, at exactly the right time?

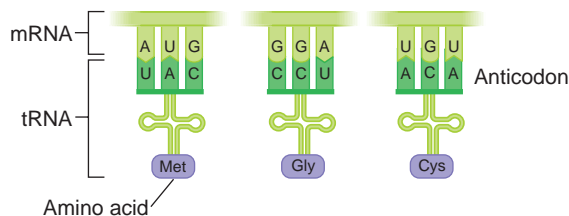
Jacob and Monod discovered that a modified form of lactose “turned on” the genes whose encoded proteins break it down. They named the set of genes that are coordinately controlled an operon, writing in 1961, *The genome contains not only a series of blueprints, but a coordinated program of protein synthesis and means of controlling its execution.*

In bacteria, operons turn transcription of a few genes on or off. In more complex organisms, different cell types express different subsets of genes. To manage this, groups of proteins called **transcription factors** come together, forming an apparatus that binds DNA at certain sequences and initiates transcription at specific sites on chromosomes. (Bacterial regulatory proteins are also called transcription factors.) The transcription factors, activated by signals from outside the cell such as hormones and growth factors, set the stage for transcription by forming a pocket for RNA polymerase—the enzyme that builds an RNA chain.

Several types of transcription factors interact to transcribe a gene. Because transcription factors are proteins, they themselves are gene-encoded. The DNA sequences that transcription factors bind may be located near the genes they control, or as far



**Figure 10.5 Transfer RNA.** (a) Certain nucleotide bases within a tRNA hydrogen bond with each other to give the molecule a “cloverleaf” conformation that can be represented in two dimensions. The darker bases at the top form the anticodon, the sequence that binds a complementary mRNA codon. Each tRNA terminates with the sequence CCA, where a particular amino acid covalently bonds. Three-dimensional representations of a tRNA (b) and (c) depict the loops that interact with the ribosome.



**Figure 10.6 A tRNA with a particular anticodon sequence always binds the same type of amino acid.**

as 40,000 bases away. DNA may form loops so that the genes encoding proteins that interact come near each other for transcription. Other proteins in the nucleus may help bring certain genes and their associated transcription factors in close proximity.

Many transcription factors have regions in common, called motifs, that fold into similar conformations. These motifs enable the transcription factor to bind DNA. They have very colorful names, such as “helix-turn-helix,” “zinc fingers,” and “leucine zippers,” that reflect their distinctive shapes.

The human genome encodes at least 2,000 types of transcription factors. Overall, they control gene expression and link the genome to the environment. For example, lack of oxygen, such as from choking or smoking, sends signals that activate transcription factors to turn on dozens of genes

that enable cells to handle the stress of low-oxygen conditions.

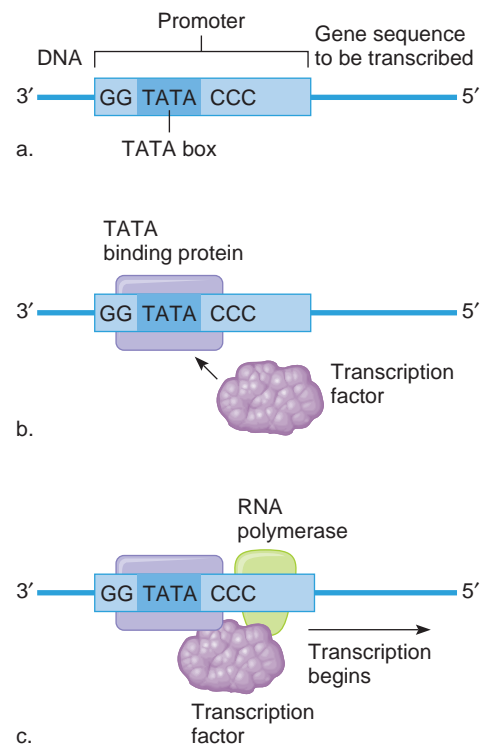
Mutations in transcription factor genes can have wide-ranging effects, because the factors control many genes. An “In Their Own Words” essay in chapter 18 describes a family cancer syndrome caused by loss of a transcription factor.

## Steps of Transcription

Transcription and translation are each described in three steps: initiation, elongation, and termination.

How do transcription factors and RNA polymerase (RNAP) “know” where to bind to DNA to begin transcribing a specific gene? In transcription initiation, transcription factors and RNA polymerase are attracted to a **promoter**, which is a special sequence that signals the start of the gene. Signals from outside the cell alter the chromatin structure in a way that exposes the promoter of a gene whose transcription is required under the particular conditions (see figure 11.8).

**Figure 10.7** shows a simplified view of transcription factor binding, which sets up a site called a preinitiation complex to receive RNA polymerase. The first transcription factor to bind, called a TATA binding protein, is attracted to a DNA sequence called a TATA box—the base sequence TATA



**Figure 10.7 Setting the stage for transcription to begin.** (a) Proteins that initiate transcription recognize specific sequences in the promoter region of a gene. (b) A binding protein recognizes the TATA region and binds to the DNA. This allows other transcription factors to bind. (c) The bound transcription factors form a pocket that allows RNA polymerase to bind and begin making RNA.

surrounded by long stretches of G and C. Once the first transcription factor binds, it attracts others in groups, and finally RNA polymerase joins the complex, binding just in front of the start of the gene sequence. The assembly of these components is transcription initiation.

In the next stage, transcription elongation, enzymes unwind the DNA double helix locally, and free RNA nucleotides bond with exposed complementary bases on the DNA template strand (see figure 10.2). RNA polymerase adds the RNA nucleotides in the sequence the DNA specifies, moving along the DNA strand in a 3′ to 5′ direction, synthesizing the RNA molecule in a 5′ to 3′ direction. A terminator sequence in the DNA indicates where the gene’s RNA-encoding region ends. When this spot is reached, the third stage, transcription termination, occurs (**figure 10.8**). A



typical rate of transcription in humans is 20 bases per second.

RNA is typically transcribed using only the gene's template strand. However, different genes on the same chromosome may be transcribed from different strands of the double helix. The coding strand of the DNA is so-called because its sequence is identical to that of the RNA, except with thymine (T) in place of uracil (U). Several RNAs may be transcribed from the same DNA template strand simultaneously (**figure 10.9**). Since mRNA is short-lived, with about half of it degraded every 10 minutes, a cell must constantly transcribe certain genes to maintain supplies of essential proteins.

To determine the sequence of RNA bases transcribed from a gene, write the RNA bases that are complementary to the template DNA strand, using uracil opposite adenine. For example, a DNA template strand that has the sequence

C C T A G C T A C

is transcribed into RNA with the sequence

G G A U C G A U G

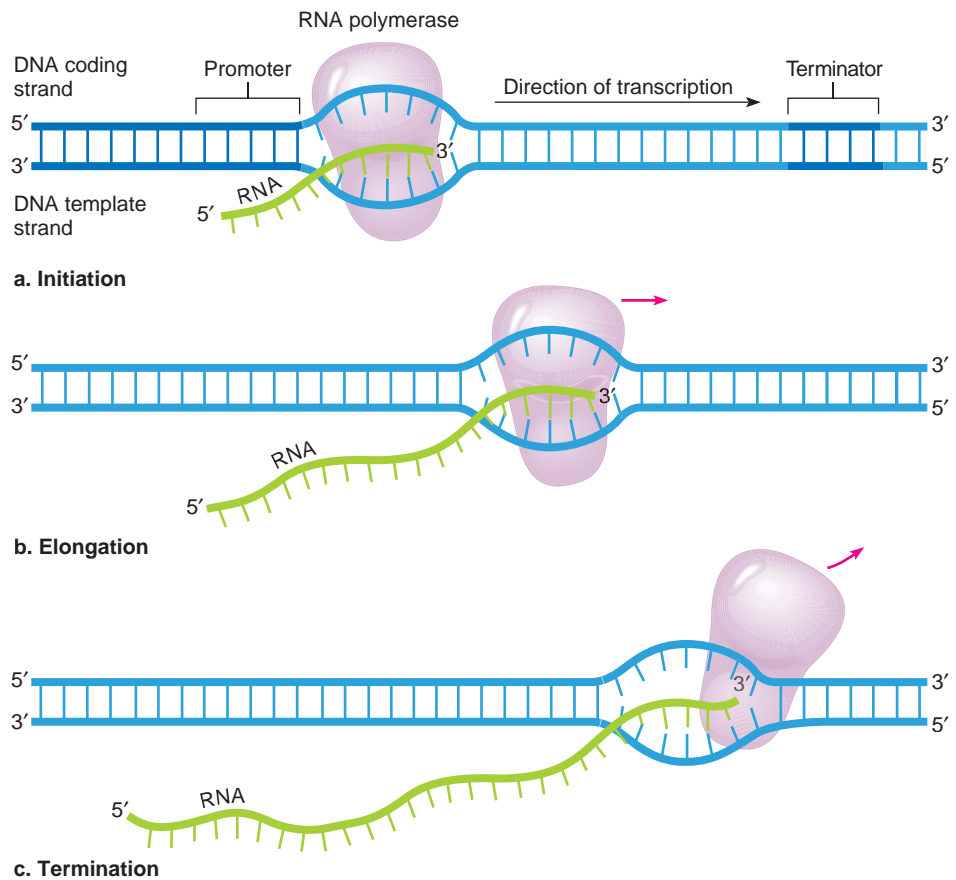
and the coding DNA sequence is

G G A T C G A T G.

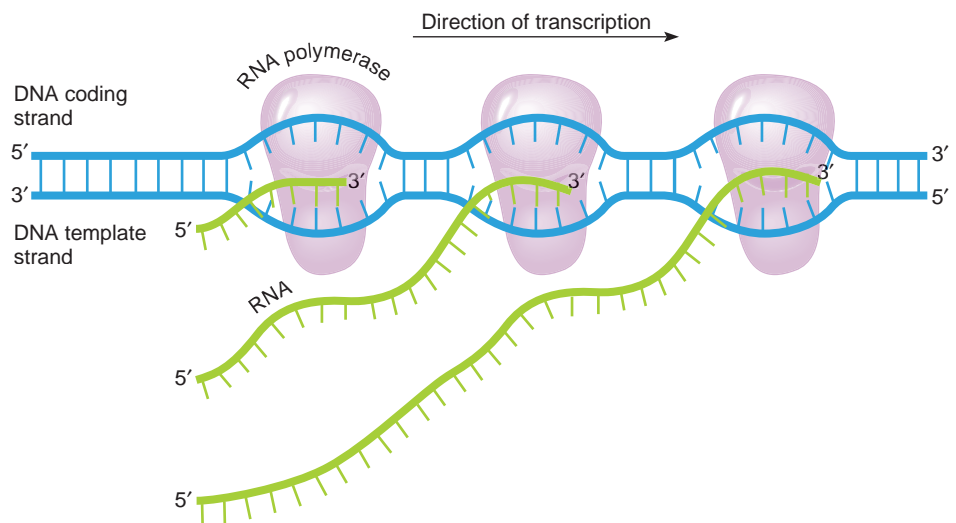
## RNA Processing

In bacteria, RNA is translated into protein as soon as it is transcribed from DNA because a nucleus does not physically separate the two processes. In eukaryotic cells, mRNA must first exit the nucleus to enter the cytoplasm, where organelles of the secretory pathway assist protein synthesis. Messenger RNA is altered before it participates in protein synthesis in these more complex cells.

First, after mRNA is transcribed, a short sequence of modified nucleotides, called a cap, is added to the 5' end of the molecule. The cap consists of a backwardly inserted guanine (G), which attracts an enzyme that adds methyl groups ( $\text{CH}_3$ ) to the G and one or two adjacent nucleotides. This methylated cap is a recognition site for protein synthesis. At the 3' end, a special polymerase adds about 200 adenines, forming a "poly A tail." The poly A tail is necessary for protein synthesis to begin, and may also stabilize the mRNA so that it stays intact.



**Figure 10.8 Transcription of RNA from DNA.** Transcription occurs in three stages: initiation, elongation, and termination. Initiation is the control point that determines which genes are transcribed. RNA nucleotides are added during elongation. A terminator sequence in the gene signals the end of transcription.



**Figure 10.9 Many identical copies of RNA are simultaneously transcribed.** Usually 100 or more DNA bases lie between RNA polymerases.

Further changes occur to the capped, poly A tailed mRNA before it is translated into protein. Parts of mRNAs called **introns** (short for “intervening sequences”) that were transcribed are removed. The ends of the remaining molecule are spliced together before the mRNA is translated. The parts of mRNA that remain and are translated are called **exons** (figure 10.10).

Once introns are spliced out, enzymes check, or proofread, the remaining mRNA. Messenger RNAs that are too short or too long may be held in the nucleus. Proofreading also monitors tRNAs, ensuring that they assume the correct conformation.

Prior to intron removal, the mRNA is called pre-mRNA. Introns control their own removal. They associate with certain proteins to form small nuclear ribonucleoproteins (snRNPs), or “snurps.” Four snurps form a structure called a spliceosome that cuts introns out and attaches exons to form the mature mRNA that exits the nucleus. The introns function as ribozymes in this process, cutting themselves out of the RNA.

Introns range in size from 65 to 10,000 or more bases; the average intron is 3,365

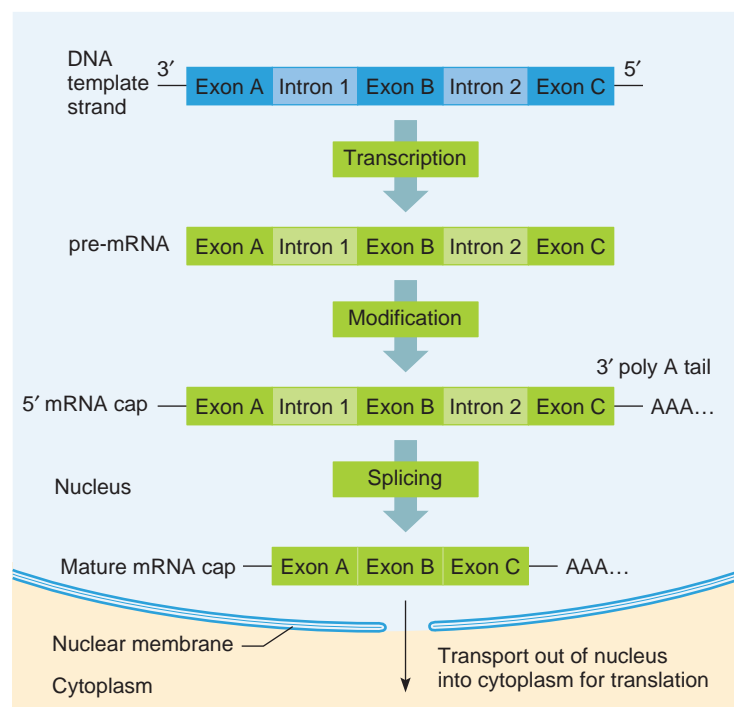
bases. The average exon, in contrast, is only 145 bases long. The number, size, and organization of introns vary from gene to gene. The coding portion of the average human gene is 1,340 bases, whereas the average total size of a gene is 27,000 bases. The dystrophin gene is 2,500,000 bases, but its corresponding mRNA sequence is only 14,000 bases! The gene contains 80 introns.

The discovery of introns in the 1970s surprised geneticists, who had thought genes were like sentences in which all of the information has meaning. At first, some geneticists called introns “junk DNA.” Introns are so common, though, that they must have a function, or they would not have persisted through evolution. Said one speaker at a genomics conference, “Anyone who still thinks that introns have no function, please volunteer to have them removed, so we can see what they do.” He had no takers.

We do not know why some genes have introns and some do not. Introns may be ancient genes that have lost their original function, or they may be remnants of the DNA of viruses that once infected the cell. Combining genes in discrete pieces, which

an intron/exon organization makes possible, may be one way that our genome maximized its informational content over evolutionary time. Introns may have enabled exons to combine in different ways. In fact, the accessing of the information in the human genome may not be a gene-by-gene phenomenon, but instead a complex utilization of gene pieces. Jacob and Monod’s statement about the “coordinated program of protein synthesis” was not only ahead of its time, but an understatement!

Another complexity is that for most human genes, mRNA is cut to different sizes in different tissues, or at different stages of development. This **alternate splicing** may explain how cell types use the same protein in slightly different ways in different tissues (see figure 11.12). For example, a protein that transports fats is shorter in the small intestine, where it carries dietary fats, than it is in the liver, where it carries fats made in the body.



**Figure 10.10 Messenger RNA processing—the maturing of the message.**

Several steps process pre-mRNA into mature mRNA. First, a large region of DNA containing the gene is transcribed. Then a modified nucleotide cap and poly A tail are added and introns are spliced out. Finally, the intact, mature mRNA is sent out of the nucleus.

## Key Concepts

1. RNA is single-stranded, has uracil instead of thymine and ribose instead of deoxyribose, and has different functions than DNA.
2. Messenger RNA transmits information to build proteins. Each three mRNA bases in a row form a codon that specifies a particular amino acid.
3. Ribosomal RNA and proteins form ribosomes, which physically support protein synthesis and help catalyze bonding between amino acids.
4. Transfer RNAs connect mRNA codons to amino acids.
5. Bacterial operons are simple gene control systems. In more complex organisms, cascades of transcription factors control gene expression.
6. RNA polymerase inserts complementary RNA bases opposite the DNA template strand.
7. Messenger RNA (mRNA) gains a modified nucleotide cap and a poly A tail.
8. Introns are transcribed and cut out, and exons are reattached. Introns are common and large in human genes.
9. Certain genes are processed into different-sized RNAs in different cell types.

## 10.2 Translation of a Protein

Transcription copies the information in DNA into the complementary language of RNA. The next step is translating mRNA into the precise sequence of amino acids that forms a protein. Particular mRNA codons correspond to particular amino acids (**figure 10.11**). This correspondence between the chemical languages of mRNA and protein is the **genetic code**.

Francis Crick hypothesized that an “adaptor” molecule would enable the RNA message to attract and link amino acids into proteins. He envisioned “*20 different kinds of adaptor molecule, one for each amino acid, and 20 different enzymes to join the amino acids to their adaptors.*” In the 1960s, researchers deciphered the genetic code, determining which mRNA codons correspond to which amino acids.

The news media often mention the recent deciphering of the “human genetic code.” This term is incorrect. The genetic code is not unique to humans, and it was cracked decades ago. The code is the correspondence between nucleic acid triplet and amino acid, not the sequence itself.

### Deciphering the Genetic Code

The researchers who deciphered the genetic code used logic and experiments. More recently, annotation of the human genome sequence has confirmed and extended the earlier work, revealing new nuances in the genetic code. To understand how the genetic

code works, it is helpful to ask the questions researchers asked in the 1960s.

#### Question 1—How Many RNA Bases Specify One Amino Acid?

Because the number of different protein building blocks (20) exceeds the number of different mRNA building blocks (4), each codon must include more than one mRNA base. If a codon consisted of only one mRNA base, then codons could specify only four different amino acids, one corresponding to each of the four bases: A, C, G, and U. If each codon consisted of two bases, then only 16 ( $4^2$ ) different amino acids could be specified, one corresponding to each of the 16 possible combinations of two RNA bases. If a codon consisted of three bases, then the genetic code could specify as many as 64 ( $4^3$ ) different amino acids, sufficient to encode the 20 different amino acids that make up proteins. Therefore, the minimum number of bases in a codon is three.

Francis Crick and his coworkers conducted experiments on a type of virus called T4 that confirmed the triplet nature of the genetic code. They exposed the virus to chemicals that add or remove one, two, or three bases, and examined a viral gene with a sequence and protein product they knew. Altering the sequence by one or two bases produced a different amino acid sequence, because it disrupted the **reading frame**, which is the sequence of amino acids encoded from a certain starting point in a DNA sequence. However, adding or deleting three con-

tiguous bases added or deleted only one amino acid in the protein without disrupting the reading frame. The rest of the amino acid sequence was retained. The code, the researchers deduced, is triplet (**figure 10.12**).

Further experiments confirmed the triplet nature of the genetic code. Adding a base at one point in the gene and deleting a base at another point disrupted the reading frame only between these sites. The result was a protein with a stretch of the wrong amino acids, like a sentence with a few words in the middle that are misspelled.

#### Question 2—Does the Information in a DNA Sequence Overlap?

Consider the hypothetical mRNA sequence:

AUGCCCAAG

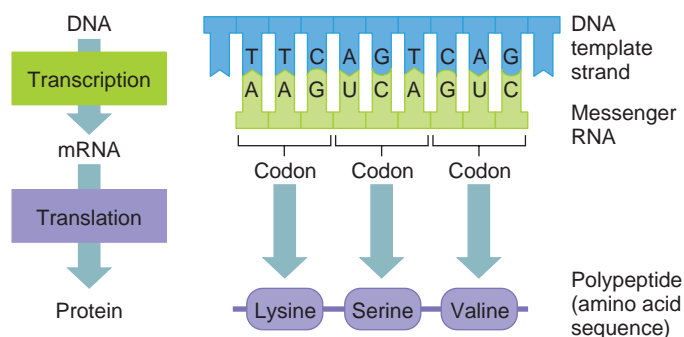
If the genetic code is triplet and a DNA sequence is “read” in a nonoverlapping manner, then this sequence has only three codons and specifies three amino acids:

AUGCCCAAG  
AUG (methionine)  
CCC (proline)  
AAG (lysine)

If the DNA sequence is overlapping, however, the sequence specifies seven codons:

AUGCCCAAG  
AUG (methionine)  
UGC (cysteine)  
GCC (alanine)  
CCC (proline)  
CCA (proline)  
CAA (glutamine)  
AAG (lysine)

An overlapping DNA sequence seems to pack maximal information into a limited number of bases, but this would constrain protein structure because certain amino acids must always follow certain others. For example, AUG would always be followed by an amino acid whose codon begins with UG. This does not happen. Therefore, the protein-encoding DNA sequence is not overlapping.




**Figure 10.11 From DNA to RNA to protein.** Messenger RNA is transcribed from a locally unwound portion of DNA. In translation, transfer RNA matches mRNA codons with amino acids. Table 10.5 lists the codon–amino acid combinations that make up the genetic code.



### Size of a genetic code word (codon)

<b>Original RNA sequence</b>	GAC GAC GAC GAC GAC GAC GAC ...
Amino acid sequence	Asp Asp Asp Asp Asp Asp Asp
<b>One base added</b>	GAC <b>G</b> GA CGA CGA CGA CGA CGA ...
Amino acid sequence altered	Asp Gly Arg Arg Arg Arg Arg
<b>Two bases added</b>	GAC <b>UG</b> G ACG ACG ACG ACG ACG ACG ...
Amino acid sequence altered	Asp Trp Thr Thr Thr Thr Thr
<b>Three bases added</b>	GAC <b>UUG</b> GAC GAC GAC GAC GAC GAC ...
Amino acid sequence altered and then restored	Asp Leu Asp Asp Asp Asp Asp

 = Wrong triplet

**Figure 10.12 Three at a time.** Adding or deleting one or two nucleotides in a DNA sequence results in a frameshift that disrupts the encoded amino acid sequence. However, adding or deleting three bases does not disrupt the reading frame. Therefore, the code is triplet. This is a simplified representation of the Crick experiment. First a G is added, then a U, then another U so that the altered codons are GGA, UGG, and UUG, corresponding to the amino acids glycine, tryptophan, and leucine. (Table 10.5 includes the full names of the amino acids abbreviated here.)

### Question 3—Can mRNA Codons Specify Anything Other Than Amino Acids?

Chemical analysis eventually showed that the genetic code includes directions for starting and stopping translation. The codon AUG signals “start,” and the codons UGA, UAA, and UAG signify “stop.” If the genetic code is compared to a sentence, the “start” codon is like the capital letter that begins the sentence, and the “stop” codon is like the period that ends the sentence. Another form of “punctuation,” a short sequence of bases at the start of each mRNA, enables the mRNA to hydrogen bond with rRNA in a ribosome. It is called a leader sequence.

### Question 4—Do All Species Use the Same Genetic Code?

All species use the same mRNA codons to specify the same amino acids. This “universality” of the genetic code is evidence that all life evolved from a common ancestor.

No other mechanism as efficient at directing cellular activities has emerged and persisted.

The only known exceptions to the universality of the genetic code are a few codons in mitochondria and in certain single-celled eukaryotes (ciliated protozoa). These deviations may be tolerated because they do not affect the major repositories of DNA. The mitochondrial genome is small, and the affected ciliated protozoa have a second, smaller nucleus that houses some genes with one or two alternate codon-amino acid associations. In both cases, the major DNA sites adhere to the universal genetic code. Some types of single-celled organisms translate a stop codon into a twenty-first type of amino acid. Overall, however, the genetic code is considered universal.

### Question 5—Which Codons Specify Which Amino Acids?

In 1961, Marshall Nirenberg and Heinrich Matthaei at the National Institutes of Health

began deciphering which codons specify which amino acids, using a precise and logical series of experiments. First they synthesized mRNA molecules in the laboratory. Then they added them to test tubes that contained all the chemicals and structures needed for translation, extracted from *E. coli* cells. Which amino acid would each synthetic RNA specify?

The first synthetic mRNA they made had the sequence UUUUUU... In the test tube, this was translated into a peptide consisting entirely of one amino acid type: phenylalanine. This was the first entry in the genetic code dictionary: The codon UUU specifies the amino acid phenylalanine. The next experiments revealed that AAA codes for the amino acid lysine and CCC for proline. (GGG was unstable, so this part of the experiment could not be done.)

Other researchers synthesized chains of alternating bases. Synthetic mRNA of sequence AUAUAU... introduced codons AUA and UAU. When translated, the mRNA yielded an amino acid sequence of alternating isoleucines and tyrosines. But was AUA the code for isoleucine and UAU for tyrosine, or vice versa? Another experiment with a more complex sequence answered the question.

The mRNA UUUAUAUUUAUA, when translated from the first U of a UUU, encoded alternating phenylalanine and isoleucine. Because the first experiment had showed that UUU codes for phenylalanine, the researchers deduced that AUA must code for isoleucine. If AUA codes for isoleucine, then UAU must code for tyrosine (**table 10.4**).

By the end of the 1960s, researchers had deciphered the entire genetic code (**table 10.5**). Sixty of the possible 64 codons specify particular amino acids, three indicate “stop,” and one encodes both the amino acid methionine and “start.” This means that some amino acids are specified by more than one codon. For example, both UUU and UUC encode phenylalanine. Different codons that specify the same amino acid are termed **synonymous codons**, just as synonyms are words with the same meaning. The genetic code is said to be degenerate because most amino acids are not uniquely specified. Synonymous codons often differ from one another by the base in the third position. The corresponding base of a tRNA’s anticodon is called the “wobble” position because it can bind to more than

one type of base in synonymous codons. The degeneracy of the genetic code protects against mutation, because changes in the DNA that substitute a synonymous codon do not alter the protein's amino acid sequence. **Nonsynonymous codons** encode different amino acids.

Deciphering the genetic code revealed the “rules” that essentially govern life at the cellular level. Because in the 1950s and 1960s molecular genetics was still a very young science, the code breakers came largely from the ranks of chemistry, physics, and math. Some of the more exuberant

personalities organized an “RNA tie club” and inducted a member whenever someone added a piece to the puzzle of the genetic code, anointing him (there were no prominent hers) with a tie and tie pin emblazoned with the structure of the specified amino acid.

The human genome project picked up where the genetic code experiments of the 1960s left off by identifying the DNA sequences that are transcribed into tRNAs. That is, 61 different tRNAs could theoretically exist, one for each codon that specifies an amino acid (the 64 triplets minus 3 stop codons). However, only 49 different genes encode tRNAs. This is because the same type of tRNA can detect synonymous codons that differ only in whether the wobble (third) position is U or C. The same type of tRNA, for example, binds to both UUU and UUC codons, which specify the amino acid phenylalanine. Synonymous codons ending in A or G

**Table 10.4**  
Deciphering RNA Codons and the Amino Acids They Specify

Synthetic RNA	Encoded Amino Acid Chain	Puzzle Piece
UUUUUUUUUUUUUUUUUUUU	Phe-Phe-Phe-Phe-Phe-Phe	UUU = Phe
AAAAAAAAAAAAAAAAAAAA	Lys-Lys-Lys-Lys-Lys-Lys	AAA = Lys
GGGGGGGGGGGGGGGGGGGG	Gly-Gly-Gly-Gly-Gly-Gly	GGG = Gly
CCCCCCCCCCCCCCCCCCCC	Pro-Pro-Pro-Pro-Pro-Pro	CCC = Pro
AUAUAUAUAUAUAUAUAU	Ile-Tyr-Ile-Tyr-Ile-Tyr	AUA = Ile or Tyr UAU = Ile or Tyr
UUUAUAUUUAUAUUUAUA	Phe-Ile-Phe-Ile-Phe-Ile	AUA = Ile UAU = Tyr

**Table 10.5**  
The Genetic Code

Second Letter						
First Letter	U	C	A	G	Third Letter	
	UUU } Phenylalanine (Phe) UUC } UUA } Leucine (Leu) UUG }	UCU } UCC } Serine (Ser) UCA } UCG }	UAU } Tyrosine (Tyr) UAC } UAA "stop" UAG "stop"	UGU } Cysteine (Cys) UGC } UGA "stop" UGG Tryptophan (Trp)		
	CUU } CUC } Leucine (Leu) CUA } CUG }	CCU } CCC } Proline (Pro) CCA } CCG }	CAU } Histidine (His) CAC } CAA } Glutamine (Gln) CAG }	CGU } CGC } Arginine (Arg) CGA } CGG }		
	AUU } AUC } Isoleucine (Ile) AUA } AUG Methionine (Met) and "start"	ACU } ACC } Threonine (Thr) ACA } ACG }	AAU } Asparagine (Asn) AAC } AAA } Lysine (Lys) AAG }	AGU } Serine (Ser) AGC } AGA } Arginine (Arg) AGG }		
	GUU } GUC } Valine (Val) GUA } GUG }	GCU } GCC } Alanine (Ala) GCA } GCG }	GAU } Aspartic acid (Asp) GAC } GAA } Glutamic acid (Glu) GAG }	GGU } GGC } Glycine (Gly) GGA } GGG }		

The genetic code consists of mRNA triplets and the amino acids that they specify.

use different tRNAs. Sequencing of other genomes reveals that some types of organisms preferentially use particular codons for amino acids specified by more than one type of codon. Researchers do not yet understand the significance, if any, of such “codon usage bias.”

## Building a Protein

Protein synthesis requires mRNA, tRNA molecules carrying amino acids, ribosomes, energy-storing molecules such as adenosine triphosphate (ATP) and guanosine triphosphate (GTP), and various protein factors. These pieces meet in a stage called translation initiation (**figure 10.13**).

First, the mRNA leader sequence forms hydrogen bonds with a short sequence of rRNA in a small ribosomal subunit. The first mRNA codon to specify an amino acid is always AUG, which attracts an initiator tRNA that carries the amino acid

methionine (abbreviated *met*). This methionine signifies the start of a polypeptide. The small ribosomal subunit, the mRNA bonded to it, and the initiator tRNA with its attached methionine form the initiation complex at the appropriate AUG codon of the mRNA.

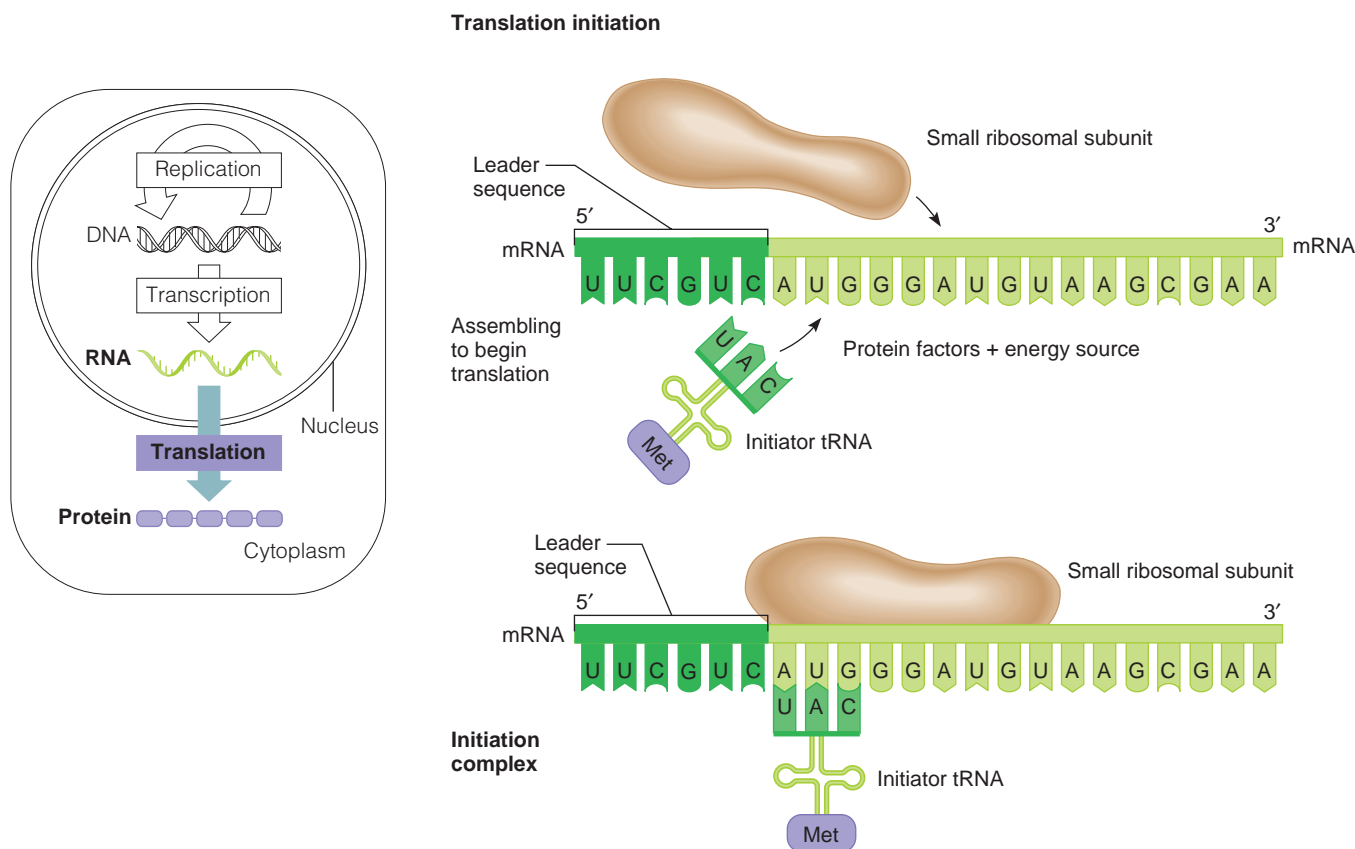
To start the next stage, elongation, a large ribosomal subunit attaches to the initiation complex. The codon adjacent to the initiation codon (AUG), which is GGA in **figure 10.14**, then bonds to its complementary anticodon, which is part of a free tRNA that carries the amino acid glycine. The two amino acids (*met* and *gly* in the example), still attached to their tRNAs, align.

The part of the ribosome that holds the mRNA and tRNAs together can be described as having two sites. The positions of the sites on the ribosome remain the same with respect to each other as translation proceeds, but they cover different parts of the mRNA as the ribosome

moves. The P site holds the growing amino acid chain, and the A site right next to it holds the next amino acid to be added to the chain. In figure 10.14, when the forming protein consists of only the first two amino acids, *met* occupies the P site and *gly* the A site.

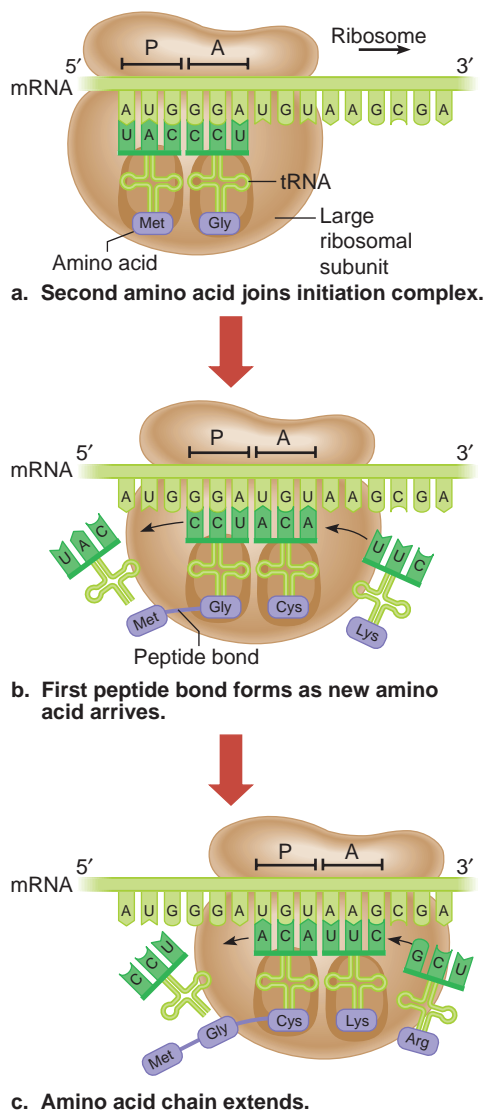
With the help of rRNA that functions as a ribozyme, the amino acids link by forming a specific type of chemical bond called a peptide bond. Then the first tRNA is released. It will pick up another amino acid of the same type and be used again. Special enzymes ensure that tRNAs always pick up the correct amino acids. This step is crucial to the accuracy of translation. The ribosome and its attached mRNA are now bound to a single tRNA, with two amino acids extending from it at the P site. This is the start of a polypeptide.

Next, the ribosome moves down the mRNA by one codon. The region of the mRNA that was at the A site is thus now



**Figure 10.13** Translation begins as the initiation complex forms. Initiation of translation brings together a small ribosomal subunit, mRNA, and an initiator tRNA, and aligns them in the proper orientation to begin translation.





**Figure 10.14 Building a polypeptide.**

(a) A large ribosomal subunit binds to the initiation complex, and a tRNA bearing a second amino acid (glycine, in this example) forms hydrogen bonds between its anticodon and the mRNA's second codon at the A site. The first amino acid, methionine, occupies the P site. (b) The methionine brought in by the first tRNA forms a peptide bond with the amino acid brought in by the second tRNA, and a third tRNA arrives, in this example carrying the amino acid cysteine. (c) A fourth amino acid is linked to the growing polypeptide chain. The process continues until a termination codon is reached.

at the P site. A third tRNA enters, corresponding to the next codon, carrying its amino acid (*cys* in figure 10.14b). This third amino acid aligns with the other two and forms a peptide bond to the second amino acid in the growing chain, now extending from the P site. The tRNA attached to the second amino acid is released and recycled. The polypeptide continues to build, one amino acid at a time. Each piece is brought in by a tRNA whose anticodon corresponds to a consecutive mRNA codon as the ribosome moves down the mRNA (figure 10.14c).

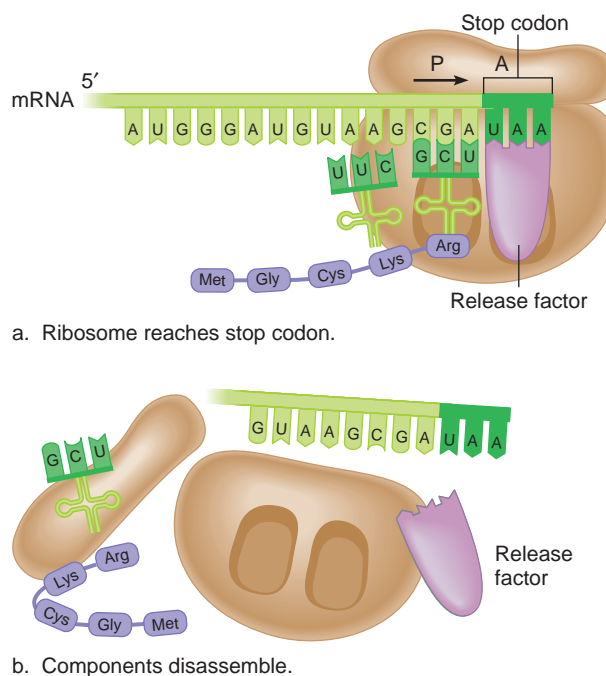
Elongation halts when the A site of the ribosome has a “stop” codon (UGA, UAG, or UAA), because no tRNA molecules correspond to it. A protein release factor starts to free the polypeptide. The last tRNA leaves the ribosome, the ribosomal subunits separate and are recycled, and the new polypeptide is released (figure 10.15).

Protein synthesis is economical. A cell can produce large amounts of a particular protein from just one or two copies of a gene. A plasma cell in the immune system, for example, manufactures 2,000 identical

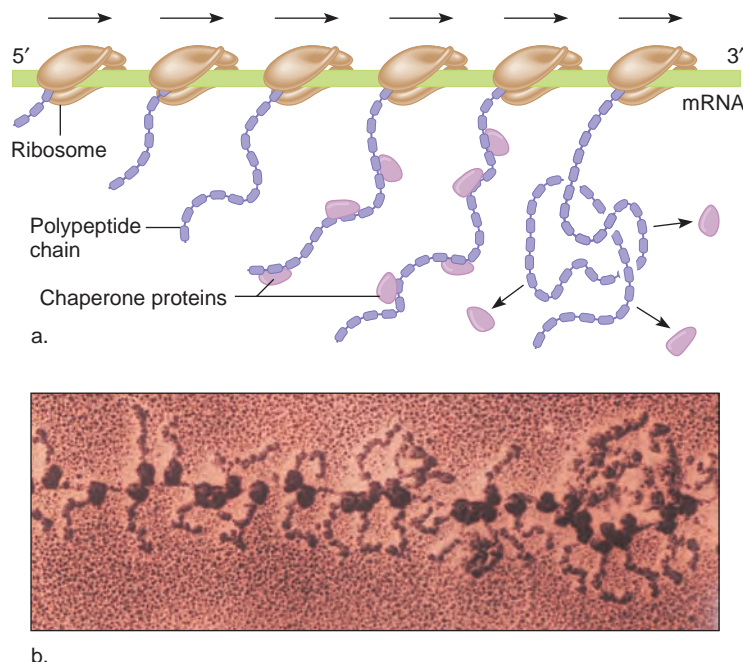
antibody molecules per second. To mass produce proteins at this rate, RNA, ribosomes, enzymes, and other proteins are continually recycled. In addition, transcription always produces many copies of a particular mRNA, and each mRNA may bind dozens of ribosomes, as figure 10.16 shows. As soon as one ribosome has moved far enough along the mRNA to leave space, another ribosome attaches. In this way, many copies of the encoded protein are made from the same mRNA.

As complex as protein synthesis is, linking amino acids is only a first step. The chain must fold in a precise sequence of steps for the protein to assume its three-dimensional form, which is essential for it to function. Protein folding is discussed on page 191.

Some proteins undergo further alterations, called post-translational modifications, before they can function. For example insulin, which is 51 amino acids long, is initially translated as the polypeptide proinsulin, which is 80 amino acids long. Enzymes cut it to 51. Some proteins must have sugars attached for them to become functional, or polypeptides must aggregate.



**Figure 10.15 Terminating a polypeptide.** (a) A protein release factor binds to the stop codon, releasing the completed polypeptide from the tRNA and (b) freeing all of the components of the translation complex.



**Figure 10.16 Making multiple copies of a protein.** Several ribosomes can simultaneously translate a protein from a single mRNA. **(a)** These ribosomes hold different-sized polypeptides—the closer to the end of a gene, the longer the polypeptide. Proteins called chaperones help fold the polypeptide. **(b)** In the micrograph, the ribosomes on the left have just begun translation and the polypeptides are short. Further along the polypeptides are longer.

### Solving A Problem: From DNA to RNA to Protein

A good way to review how DNA replicates and uses genetic information is to follow molecular sequences from DNA to RNA to protein. DNA specifies RNAs, which work together to align amino acids to form proteins. The following table shows the relationships of the various informational molecules involved in protein synthesis.

Type of molecule	Rules and relationships
DNA coding strand	1 Coding and template strands have complementary DNA bases.
DNA template strand	2 mRNA is complement of DNA template strand, with U for T.
mRNA codons	3 mRNA is same as DNA coding strand, with U for T. 4 tRNA anticodons are complement of mRNA.
tRNA anticodons	5 tRNA anticodons are same as DNA template strand, with U for T. 6 tRNA anticodons are complement of DNA coding strand, with U for T.
Amino acids (protein)	7 tRNA translates genetic code, bringing together amino acids specified by DNA coding strand. 8 Amino acids bond to form a protein.

## Key Concepts

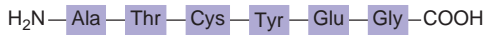
1. The genetic code is triplet, nonoverlapping, continuous, universal, and degenerate.
2. As translation begins, mRNA, tRNA with bound amino acids, ribosomes, energy molecules, and protein factors assemble. The mRNA binds to rRNA in a small ribosomal subunit. The first codon attracts a tRNA bearing methionine.
3. The large ribosomal subunit attaches and the tRNA anticodons bind to successive codons. Aligned amino acids form peptide bonds. A polypeptide forms.
4. The ribosome moves down the mRNA to the amino acid chain (the P site) and to where a new tRNA binds (the A site).
5. When the ribosome reaches a "stop" codon, protein synthesis ceases. Components are recycled.

affect protein conformation by bridging the two types of amino acids that contain them. Proteins fold in the endoplasmic reticulum.

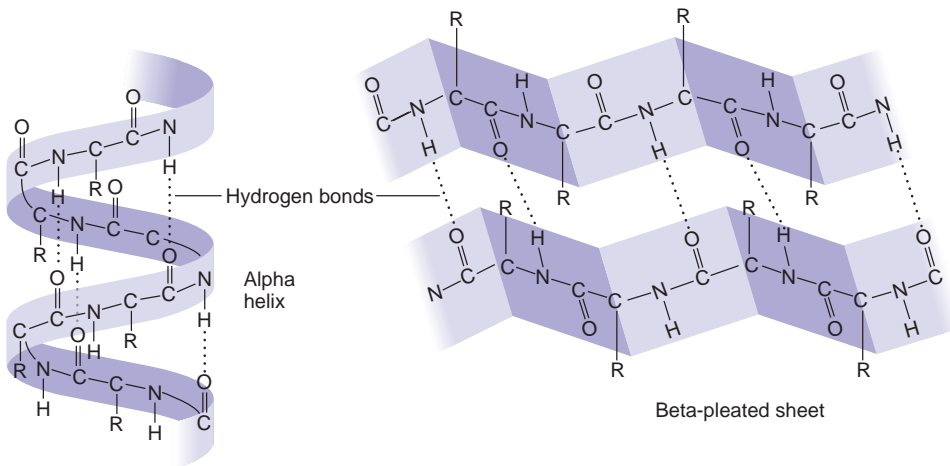
The conformation of a protein is described at several levels (**figure 10.17**). The amino acid sequence of a polypeptide chain determines its **primary (1°) structure**. Chemical attractions between amino acids that are close together in the 1° structure fold the polypeptide chain into its **secondary (2°) structure**, which may form loops, coils, barrels, helices, sheets, or other distinctive shapes. The two most common secondary structures are an alpha helix and a beta-pleated sheet. Secondary structures wind into larger **tertiary (3°) structures** as more widely separated amino acids attract or repel in response to water molecules. Finally, proteins consisting of more than one polypeptide form a **quaternary (4°) structure**. Hemoglobin, the blood protein that carries oxygen, has four polypeptide chains (see **figure 11.1**). The liver protein ferritin has 20 identical polypeptides of 200 amino acids each. In contrast, the muscle protein myoglobin is a single polypeptide chain.

## 10.3 Protein Folding

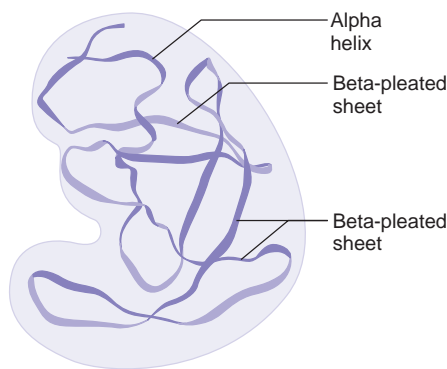
Proteins must fold into one (or more) specific three-dimensional shape(s), or conformation(s), to function. This folding occurs because of attractions and repulsions between atoms. In addition, thousands of water molecules surround a growing chain of amino acids. Because some amino acids are attracted to water and some are repelled by it, the water con-torts the protein's shape. Sulfur atoms also



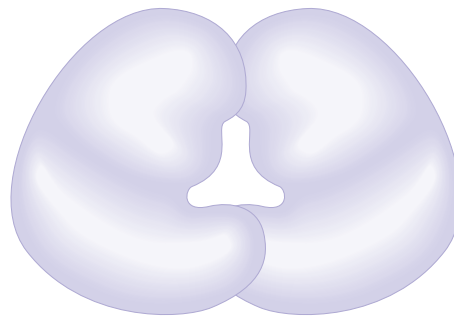
a. **Primary structure**—the sequence of amino acids in a polypeptide chain



b. **Secondary structure**—loops, coils, sheets, or other shapes formed by hydrogen bonds between neighboring carboxyl and amino groups



c. **Tertiary structure**—three-dimensional forms shaped by bonds between R groups, interactions between R groups and water



d. **Quaternary structure**—protein complexes formed by bonds between separate polypeptides

**Figure 10.17 Four levels of protein structure.** (a) The amino acid sequence of a polypeptide forms the primary structure. Each amino acid has an amino end (NH) and a carboxyl end (COOH), and each of the 20 types of amino acids is distinguished by an R group. (b) Hydrogen bonds between non-R groups create secondary structures such as helices and sheets. The tertiary structure (c) is formed when R groups interact, folding the polypeptide in three dimensions and forming a unique shape. (d) If different polypeptide units must interact to be functional, the protein has a quaternary structure.

Protein folding begins within a minute after the amino acid chain winds away from the ribosome. A small protein might contort into its final, functional form in one quick step, taking only a few microseconds. Larger proteins may fold into a series

of short-lived intermediates before assuming their final, functional forms.

Various proteins assist in this precise folding. **Chaperone proteins** stabilize partially folded regions in their correct form, and prevent a protein from getting

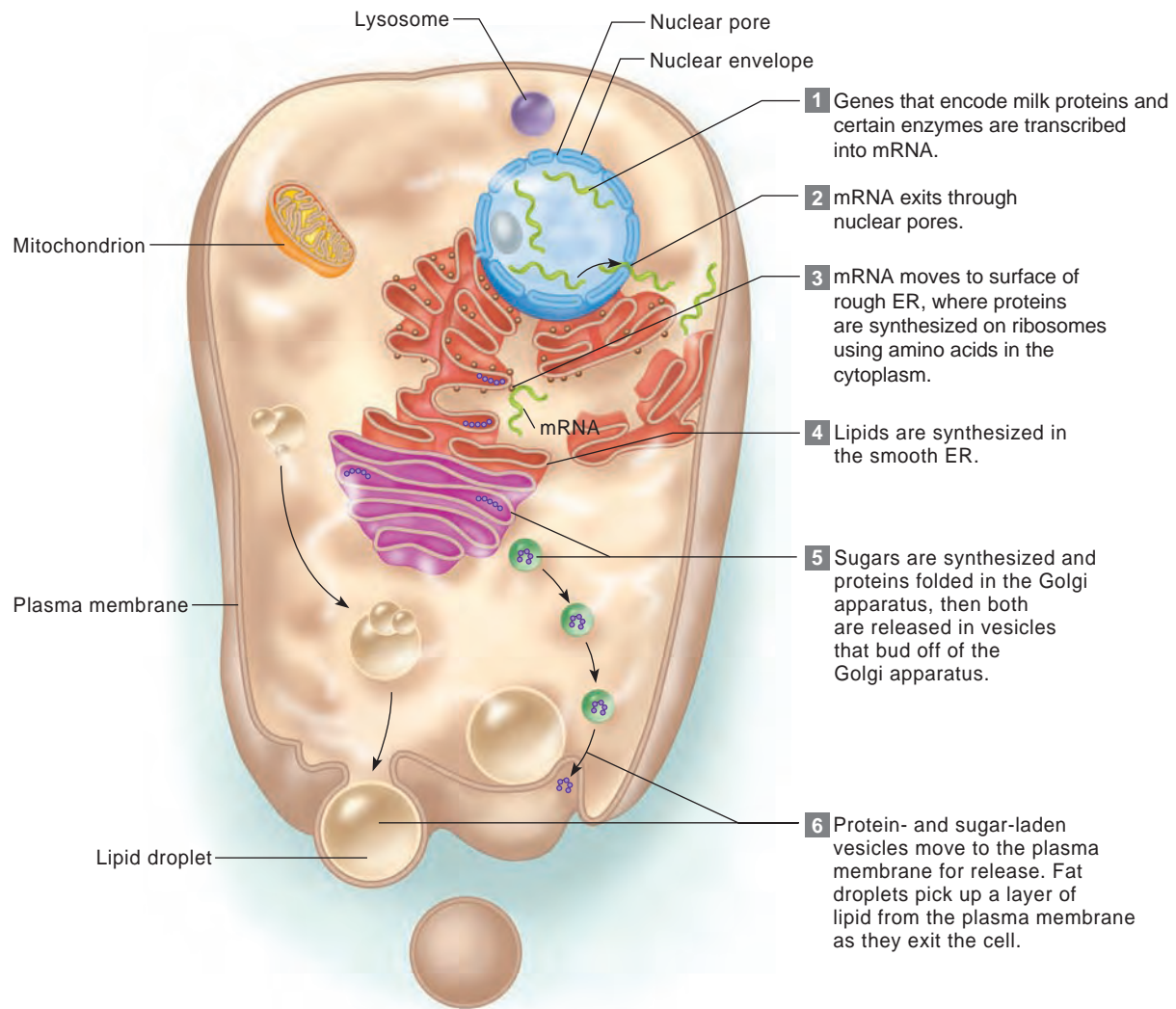
“stuck” in an intermediate form—which would be disastrous for the cell. Other proteins help new chemical bonds to form as the final shape arises, and yet others monitor the accuracy of folding. Should a protein misfold, an “unfolded protein response” occurs. Protein synthesis slows or even stops, transcription of genes that encode chaperone proteins and the other folding proteins speeds up, and proper protein folding is quickly restored. Properly folded proteins are sent into the ER tubules and packaged for transport, either to be used in the cell or secreted. Figure 2.5 is reprinted here as **figure 10.18** to review the places in the cell where transcription, translation, and secretion occur.

Misfolded proteins have a different fate than properly folded ones. They are sent out of the ER back into the cytoplasm. The misfolded proteins are “tagged” with yet another protein, called ubiquitin. A misfolded protein bearing just one ubiquitin tag may straighten and refold correctly, but a protein with more than one tag is taken to a cellular garbage disposal called a **proteasome** (**figure 10.19**). A proteasome is a tunnel-like multi-protein structure. Through it, the protein is stretched out, chopped up, and its peptide pieces degraded into amino acids.

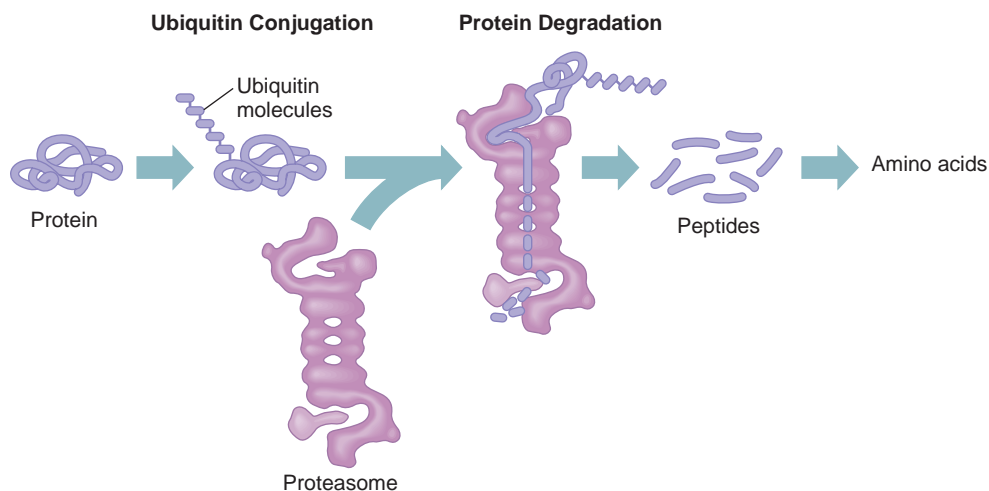
Misfolded proteins that are not destroyed can cause disease. Sickle cell disease, for example, is the result of hemoglobin that forms sheets (see **figure 12.2**) instead of the normal globular structure shown in **figure 11.1**. Some mutations that cause cystic fibrosis prevent CFTR protein from folding and anchoring in the plasma membrane, where it normally controls the flow of chloride ions. Instead, the misfolded protein builds up in the cell.

In several disorders that affect the brain, misfolded proteins—different proteins in different conditions—aggregate, forming masses that clog the proteasomes and block them from processing any malformed proteins. In Huntington disease, for example, extra glutamines in the protein huntingtin cause it to obstruct proteasomes. Misfolded proteins that clog proteasomes also form in the disorders listed in **Table 10.6**, but it isn’t always clear whether the accumulated proteins cause the disease or are a response to it.





**Figure 10.18 Sites of transcription and translation in a cell.** A look back at figure 2.5, which depicts the secretion of milk, indicates where these processes that constitute gene expression take place.



**Figure 10.19 Protein folding quality control.** Ubiquitin binds to a misfolded protein and escorts it to a proteasome. The proteasome, which is composed of several proteins, encases the misfolded protein, straightening and dismantling it.

Some of these disorders are discussed further in chapter 12.

A rare type of protein folding disorder arises in glycoproteins called prions (pronounced *pree-ons*). Diseases called transmissible spongiform encephalopathies (TSEs) result when one conformation of the prion glycoprotein (PrP) is infectious, which means that it causes others to misfold like it does (**figure 10.20** and Reading 10.1). TSEs were discovered in sheep, which develop a disease called scrapie when they eat prion-infected brains from other sheep.

Unlike other misfolded proteins that cause disease, the variant forms of prion



## Reading 10.1

### Considering Kuru

Prion diseases cause extreme weight loss and poor coordination, with other symptoms, such as dementia or relentless insomnia, reflecting the part of the brain that degenerates. These diseases are typically fatal within 18 months of symptom onset.

About 10 percent of people who suffer from prion diseases have mutations in the gene that encodes prion protein, called *PrP*. Most cases, however, are acquired. A person is exposed to prions that are in the infectious conformation, and this triggers conversion of the person's own normal prions into disease-causing ones.

A prion disease affecting humans was kuru, which struck the Foré people in a remote mountainous area of New Guinea (figure 1). In the Foré language, *kuru* means to tremble. The disease began with wobbling legs, quickly followed by trembling hands and fingers. Gradually, the entire body became wracked with shaking. A peculiar symptom was uncontrollable laughter, leading to the nickname “laughing disease.” Speech slurred and faded, thinking slowed, and after several months, the person could no longer walk or eat. Death typically came within a year.

The fact that only women and young children developed kuru at first suggested that the disease might be inherited, but D. Carleton Gajdusek, a physician who has spent much of his lifetime studying the Foré, learned that the preparation of human brain for a cannibalism ritual probably passed on the infectious prions. After the people abandoned the ritual in the 1970s, the disease gradually disappeared. Gajdusek vividly described the Foré preparation of human brains at a time when he thought the cause was viral:

**Children participated in both the butchery and the handling of cooked meat, rubbing their soiled hands in their armpits or hair, and elsewhere on their bodies. They rarely or never washed. Infection with the kuru**

**virus was most probably through the cuts and abrasions of the skin or from nose picking, eye rubbing, or mucosal injury.**

Although kuru vanished, other prion diseases surfaced. In the 1970s and 1980s, several people acquired Creutzfeldt-Jakob disease (CJD). This time, the route of transmission was either through corneal transplants, in which infectious prions entered the brain through the optic nerve, or from human growth hormone taken from cadavers and used to treat short stature in children. The most familiar prion disease is “mad cow disease” and the variant CJD it has caused in more than 120 people in the United Kingdom since 1995. People likely

acquired the infectious prions by eating infected beef.

Researchers have discovered that several specific polymorphisms (variants) in the *PrP* gene interact in ways that make some people resistant to prion diseases, yet others highly susceptible. These mutations are discussed further in chapter 12. The persistence of the protective gene variants, some researchers say, is evidence that cannibalism may have been common in some of our prehistoric ancestors, and that protected individuals survived. Anthropological evidence of cannibalism includes human bite marks on human bones. Several functions for normal prion protein have been suggested, including enabling bone marrow stem cells to self-renew.



**Figure 1 Kuru.** Kuru is a prion disease that affected the Foré people of New Guinea until they gave up a cannibalism ritual that spread an infectious form of prion protein.

protein have the same primary structure, but they can fold into at least eight conformations. It is a little like dropping two identical multicolored beaded necklaces. Each would fall into a different overall shape, but the sequence of bead colors would be unchanged. TSEs are known in 85 types of mammals, including humans. The affected brain becomes riddled with holes, resembling a sponge. Nerve cells die, and neuroglial cells overgrow.

The “rules” by which DNA sequences specify protein shapes are still not well understood, even as we routinely decipher the sequences of entire genomes. The straightforward linear relationship between gene and protein that emerged from the experiments of the 1960s was merely an opening chapter to the story of how a cell builds its proteins.

### Key Concepts

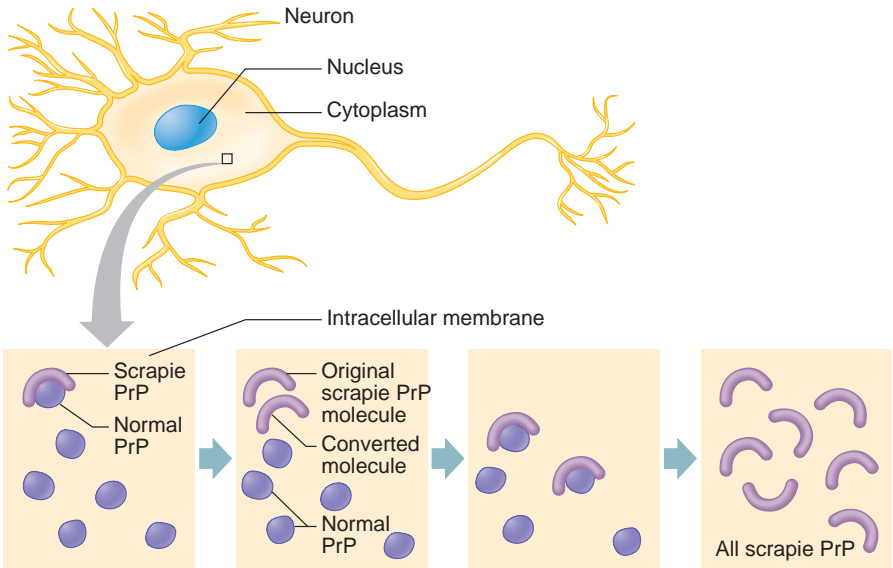
1. Protein folding begins as translation proceeds, with enzymes and chaperone proteins assisting.
2. Misfolded proteins are tagged with ubiquitin and sent through a proteasome for dismantling.
3. A protein can fold in more than one way.
4. Infectious conformations of prion proteins cause disease.

Table 10.6

Disorders Associated with Protein Misfolding

Disease	Misfolded Protein	OMIM (protein)
Alzheimer disease	amyloid beta precursor protein	104760
Familial amyotrophic lateral sclerosis	superoxide dismutase	147450
Huntington disease	huntingtin	143100
Parkinson disease	alpha synuclein	163890
Lewy body dementia	alpha synuclein	
Prion disorders	prion protein	176640

(All but Huntington disease are genetically heterogeneous; that is, abnormalities in different proteins cause similar syndromes.)



**Figure 10.20 Prions change shape.** A prion disease may begin when a single scrapie PrP contacts a normal PrP and changes it into the scrapie conformation. As the change spreads, disease results, usually with accumulated scrapie prion proteins clogging brain tissue.

## Summary

### 10.1 Transcription

1. Some DNA is **transcribed** into RNA, which is then **translated** into protein.
2. RNA is transcribed from the **template strand** of DNA. The other DNA strand is called the **coding strand**.
3. RNA is a single-stranded nucleic acid similar to DNA but containing uracil and ribose rather than thymine and deoxyribose.
4. Several types of RNA participate in protein synthesis. **Messenger RNA** (mRNA) carries a protein-encoding gene’s information.

**Ribosomal RNA** (rRNA) associates with certain proteins to form ribosomes, which physically support protein synthesis. **Transfer RNA** (tRNA) is cloverleaf-shaped, with a three-base **anticodon** that is complementary to mRNA on one end and bonds to a particular amino acid on the other end.

5. Operons control gene expression in bacteria. In more complex organisms, **transcription factors** regulate which genes are transcribed in a particular cell type.
6. Transcription begins when transcription factors help **RNA polymerase** (RNAP)

bind to a gene’s **promoter**. RNAP then adds RNA nucleotides to a growing chain, in a sequence complementary to the DNA template strand.

7. After a gene is transcribed, the mRNA receives a “cap” of modified nucleotides at the 5’ end and a poly A tail at the 3’ end.
8. Many genes do not encode information in a continuous manner. After transcription, **exons** are translated into protein and **introns** are removed. Introns may outnumber and outsize exons. Alternate splicing increases protein diversity.



## 10.2 Translation of a Protein

9. Each three consecutive mRNA bases form a **codon** that specifies a particular amino acid. The **genetic code** is the correspondence between each codon and the amino acid it specifies. Of the 64 different possible codons, 60 specify amino acids, one specifies the amino acid methionine and “start,” and three signal “stop.” Because 61 codons specify the 20 amino acids, more than one type of codon may encode a single amino acid. The genetic code is nonoverlapping, triplet, universal, and degenerate.
10. In the 1960s, researchers used logic and clever experiments using synthetic RNAs to decipher the genetic code.
11. Translation requires tRNA, ribosomes, energy-storage molecules, enzymes, and protein factors. An initiation complex forms when mRNA, a small ribosomal subunit, and a tRNA carrying methionine

join. The amino acid chain elongates when a large ribosomal subunit joins the small one. Next, a second tRNA binds by its anticodon to the next mRNA codon, and its amino acid bonds with the first amino acid. Transfer RNAs add more amino acids, forming a polypeptide. The ribosome moves down the mRNA as the chain grows. The P site bears the amino acid chain, and the A site holds the newest tRNA. When the ribosome reaches a “stop” codon, it falls apart into its two subunits and is released. The new polypeptide breaks free.

12. After translation, some polypeptides are cleaved, have sugars added, or aggregate. The cell uses or secretes the protein.

## 10.3 Protein Folding

13. A protein must fold into a particular conformation to be active and functional.
14. A protein’s **primary structure** is its amino acid sequence. Its **secondary structure**

forms as amino acids close in the primary structure attract one another. **Tertiary structure** appears as more widely separated amino acids attract or repel in response to water molecules. **Quaternary structure** forms when a protein consists of more than one polypeptide.

15. **Chaperone proteins** help conformation arise. Other proteins help new bonds form and oversee folding accuracy.
16. Ubiquitin attaches to misfolded proteins, and escorts them to **proteasomes** for dismantling. Protein misfolding is associated with certain diseases.
17. Some proteins can fold into several conformations, some of which can cause disease.
18. At least one conformation of prion protein is infectious, causing transmissible spongiform encephalopathies.

# Review Questions

1. Explain how complementary base pairing is responsible for
  - a. the structure of the DNA double helix.
  - b. DNA replication.
  - c. transcription of RNA from DNA.
  - d. the attachment of mRNA to a ribosome.
  - e. codon/anticodon pairing.
  - f. tRNA conformation.
2. A retrovirus has RNA as its genetic material. When it infects a cell, it uses enzymes to copy its RNA into DNA, which then integrates into the host cell’s chromosome. Is this flow of genetic information consistent with the central dogma? Why or why not?
3. What are the functions of these proteins?
  - a. RNA polymerase
  - b. ubiquitin
  - c. a chaperone protein
  - d. a transcription factor
4. Explain where a hydrogen bond forms and where a peptide bond forms.
5. List the differences between RNA and DNA.
6. Where in a cell do DNA replication, transcription, and translation occur?
7. How does transcription control cell specialization?
8. How can the same mRNA codon be at an A site on a ribosome at one time, but at a P site at another time?
9. Describe the events of transcription initiation.
10. List the three major types of RNA and their functions.
11. Describe three ways RNA is altered after it is transcribed.
12. What are the components of a ribosome?
13. Why would an overlapping genetic code be restrictive?
14. How are the processes of transcription and translation economical?
15. Explain how protein misfolding conditions and illnesses that result from abnormal transcription factors might each produce many different symptoms.
16. What factors determine how a protein folds into its characteristic conformation?
17. Why would two-nucleotide codons be insufficient to encode the number of amino acids in biological proteins?
18. How do a protein’s primary, secondary, and tertiary structures affect conformation? Which is the most important determinant of conformation?

# Applied Questions

- List the RNA sequences that would be transcribed from the following DNA template sequences.
  - TTACACTTGCTTGAGAGTC
  - ACTTGGGCTATGCTCATTA
  - GGCTGCAATAGCCGTAGAT
  - GGAATACGTCTAGCTAGCA
- Given the following partial mRNA sequences, reconstruct the corresponding DNA template sequences.
  - GCUAUCUGUCAUAAAAGAGGA
  - GUGGCGUAUUCUUUCCGGGUAGG
  - GAGGGAAUUCUUUCUACGAAGU
  - AGGAAAACCCUCUUAUUAUAGAU
- List three different mRNA sequences that could encode the following amino acid sequence:  
histidine-alanine-arginine-serine-leucine-valine-cysteine
- Write a DNA sequence that would encode the following amino acid sequence:  
valine-tryptophan-lysine-proline-phenylalanine-threonine
- In the film *Jurassic Park*, which is about cloned dinosaurs, a cartoon character named Mr. DNA talks about the billions of genetic codes in DNA. Why is this statement incorrect?
- Titin is a muscle protein named for its gargantuan size—its gene has the largest known coding sequence of 80,781 DNA bases. How many amino acids long is it?
- An extraterrestrial life form has a triplet genetic code with five different bases. How many different amino acids can this code specify, assuming no degeneracy?
- In malignant hyperthermia, a person develops a life-threateningly high fever after taking certain types of anesthetic drugs. In one family, mutation deletes three contiguous bases in exon 44. How many amino acids are missing from the protein?
- The protein that serves as a receptor that allows insulin to enter cells has a different number of amino acids in a fetus and in an adult. Explain how this may happen.

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 10** and **Web Activities** to find the website links needed to complete the following activities.

- Go to the Harvard University website. Scroll down to the lists of “noncanonical” codes in organisms other than humans. (*Noncanonical* means it differs from the universal genetic code.) Find three examples of deviations from the universal code, and list what the codon-amino acid assignment is in most organisms. (Replace the T’s on the website with the U’s to correspond to the genetic code chart in the textbook.)
- Use the Web to find out how the ubiquitin-proteasome system is overtaxed or disabled in a neurodegenerative disease

such as Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, or Lewy body dementia. (Find websites for these disorders and discuss how the mechanism involves proteasomes.)

## Case Studies and Research Results

- Five patients meet at a clinic for families in which several members have early-onset Parkinson disease. This condition causes rigidity, tremors, and other motor symptoms. Only 2 percent of cases of Parkinson disease are inherited. The five patients all have mutations in a gene that encodes the protein parkin, which has 12 exons. For each patient, indicate whether the mutation shortens, lengthens, or does not change the size of the protein.
  - Manny Filipo’s *parkin* gene is missing exon 3.
  - Frank Myer’s *parkin* gene has a duplication in intron 4.
  - Theresa Ruzi’s *parkin* gene lacks six contiguous nucleotides in exon 1.
  - Elyse Fitzsimmon’s *parkin* gene has an altered splice site between exon 8 and intron 8.
  - Scott Shapiro’s *parkin* gene is deleted.
- A research project called ENCODE (ENCyclopedia of DNA Elements) took 1 percent of the human genome and cataloged 487 genes and 2,608 mRNA transcripts. Why isn’t the number the same?

# A Second Look

- Explain how comparing DNA sequences enabled researchers to better understand the symptoms of Marfan syndrome.
- Explain how the symptoms of Marfan syndrome can result from mutation in the gene encoding either fibrillin or TGF- $\beta$
- Discuss how the use of an animal model provided information on Marfan syndrome that was not easily or ethically available from people.

Learn to apply the skills of a genetic counselor with this additional case found in the *Case Workbook in Human Genetics*:

Alpha-antitrypsin deficiency



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.





# Control of Gene Expression and Genome Architecture

## CHAPTER CONTENTS

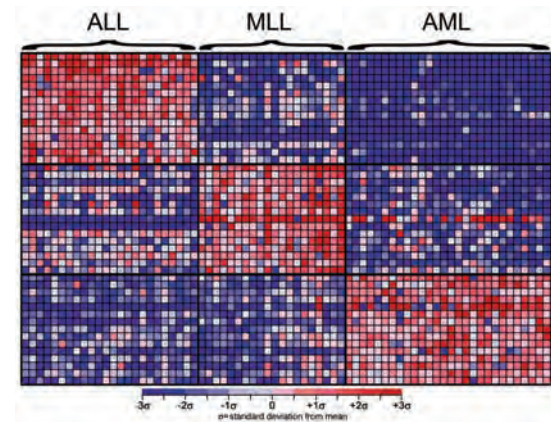
- 11.1 **Gene Expression Through Time and Tissue**
  - Globin Chain Switching
  - Building Tissues and Organs
  - Proteomics
- 11.2 **Mechanisms of Gene Expression**
  - Chromatin Remodeling
  - RNA Interference
- 11.3 **Proteins Outnumber Genes**
- 11.4 **Most of the Human Genome Does Not Encode Protein**
  - Viral DNA
  - Noncoding RNAs
  - Repeats

## UNCLOAKING A CANCER

Two children with leukemia may experience the same fatigue, fever, and bruising because their cancerous white blood cells crowd out the red blood cells and platelets in the bone marrow and blood-stream. Their cancer cells may look identical under a microscope. But at the level of gene expression—that is, the proteins in their cancer cells—the diseases may be quite different. Subtyping cancers by gene expression patterns may have great clinical consequences. This is the case for acute lymphoblastic leukemia (ALL).

Tim had ALL, but was among the 90 percent who respond to chemotherapy. At the clinic, he and his parents met a family that wasn't so lucky. Their baby daughter Emily, also diagnosed with ALL, worsened after each treatment, and she died.

Researchers at the Dana Farber Cancer Institute were concerned about the hundred or so babies in the United States each year who, like Emily, develop what seems to be ALL but do not respond to drugs that work well in others. Thinking that not all ALL cells are the same, the investigators analyzed what the cancer cells *do*, rather than how they appear. Gene expression DNA microarrays (“gene chips”) compared 12,000 genes. In sicker infants diagnosed with ALL, 1,000 genes were underexpressed and 200 overexpressed compared to the vast majority of children with ALL. The sicker children actually had an entirely different disease, named “mixed lineage leukemia,” or MLL. They respond to different drugs.



Colors represent different levels of gene expression. These leukemias—ALL, MLL, and AML—differ in gene expression patterns. The vertical columns of squares represent tumor samples, and the horizontal rows compare the activities of particular genes. Red tones indicate higher-than-normal expression and blue tones show lower-than-normal expression. The different patterns indicate distinct cancers, although the cells may look alike under a microscope. For many years, the newly recognized mixed-lineage leukemia (MLL) was considered a subtype of acute lymphoblastic leukemia (ALL), and was treated as such—with little success.

A genome is like an orchestra. Just as not all of the instruments play with the same intensity at every moment, not all genes are expressed continually at the same levels. Before the field of genomics began in the 1990s, the study of genetics proceeded one gene at a time, like hearing the separate contributions of a violin, a viola, and a flute. Many genetic investigations today, in contrast, track the crescendos of gene activity that parallel events in an organism's life. This new view has introduced the element of time to genetic analysis. Unlike the gene maps of old, which ordered genes on chromosomes, new types of maps reveal the orders of events in unfolding programs of development and response to the environment.

The discoveries of the 1950s and 1960s on DNA structure and function answered some questions about the control of gene expression while raising many more. How does a bone cell “know” to transcribe the genes that control the synthesis of collagen and not to transcribe genes that specify muscle proteins? How do the percentages of blood cell types shift when a person has leukemia? How do the activities of the many genes followed in the DNA microarray depicted in the chapter opener control the spectrum of white blood cell types, so that leukemia does not occur?

Another complexity of gene expression is that producing protein is not all that a genome does. Sequencing of the human genome revealed that protein types in the human body outnumber the genes that encode them. However, much of the genome does not encode protein at all, although nearly all of it is transcribed. Apparently RNA does much more than encode protein.

This chapter extends the discussion of DNA structure and function to consider how gene expression is controlled, as well as the peculiarities of genome architecture—that is, what DNA does besides encode protein and the RNA molecules required to synthesize protein.

## 11.1 Gene Expression Through Time and Tissue

Before DNA microarrays provided peeks at many interacting genes, investigating the

control of gene expression focused on individual, compelling examples. Following are three examples of control of gene expression at the molecular, tissue, and organ levels: hemoglobin switching during development, the composition of blood plasma, and specialization of the two major parts of the pancreas.

### Globin Chain Switching

The globin proteins that transport oxygen in the blood vividly illustrate the exquisite control of gene expression. The molecule's changing composition through development was discovered half a century ago.

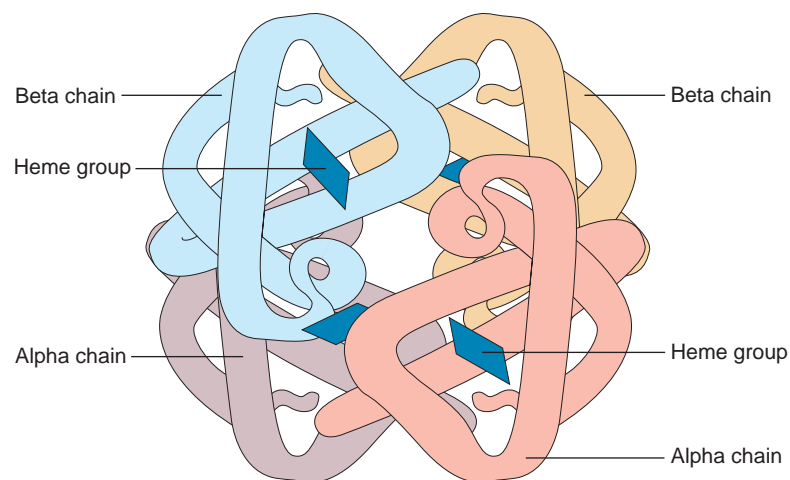
A hemoglobin molecule in an adult has four polypeptide chains, each wound into a globular conformation (**figure 11.1**). Two of the chains are 146 amino acids long and are called “beta” ( $\beta$ ). The other two chains are 141 amino acids long and are termed “alpha” ( $\alpha$ ). The genes for beta subunits are clustered on chromosome 11, and the alpha genes are grouped on chromosome 16.

The subunits of the hemoglobin molecule are replaced as the oxygen concentration in the body changes, which in turn depends upon whether oxygen arrives to an embryo or fetus through the placenta or to a newborn's lungs as he or she breathes. The chemical basis for this “globin chain switching” is that different polypeptide

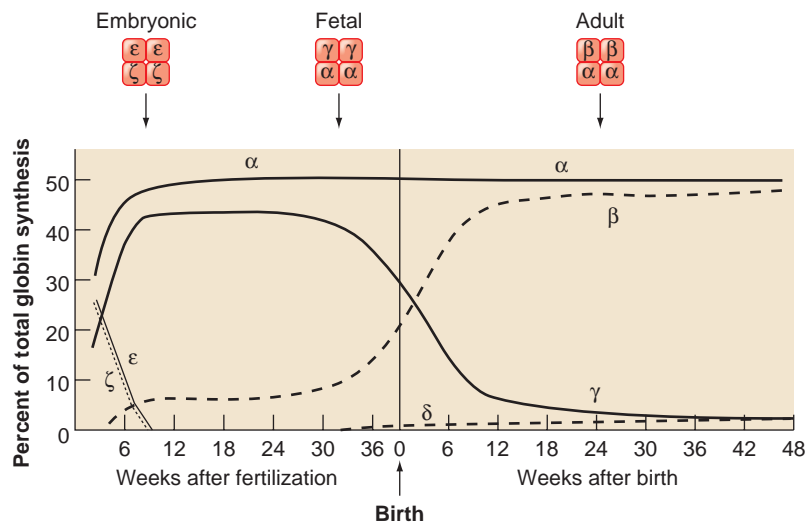
subunits attract oxygen molecules to different degrees. Parts of the globin gene clusters, called locus control regions, oversee the changes in the molecule's composition and assembly.

The subunit makeup of the hemoglobin molecule differs in the embryo, fetus, and adult (**figure 11.2**). In the embryo, as the placenta forms, hemoglobin consists first of two epsilon ( $\epsilon$ ) chains, which are in the beta globin group, and two zeta ( $\zeta$ ) chains, which are in the alpha globin group. About 4 percent of the hemoglobin in the embryo includes beta chains. This percentage gradually increases.

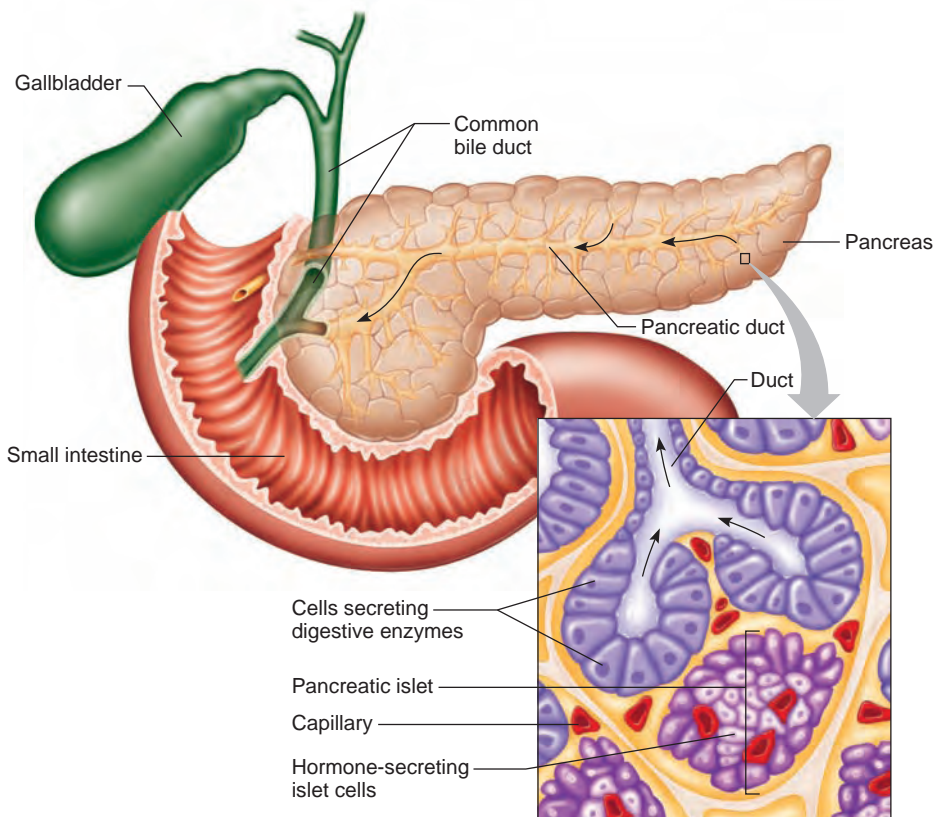
As the embryo develops into a fetus, the epsilon and zeta chains decrease in number, as gamma ( $\gamma$ ) and alpha chains accumulate. Hemoglobin consisting of two gamma and two alpha chains is called fetal hemoglobin. The gamma globin subunits bind very strongly to oxygen released from maternal red blood cells into the placenta, so that fetal blood carries 20 to 30 percent more oxygen than an adult's blood. As the fetus matures, beta chains gradually replace the gamma chains. At birth, however, the hemoglobin is not fully of the adult type—fetal hemoglobin (two gamma and two alpha chains) comprises from 50 to 85 percent of the blood. By four months of age, the proportion drops to 10 to 15 percent, and by four years, it is less than 1 percent.



**Figure 11.1 The structure of hemoglobin.** A hemoglobin molecule is made up of two globular protein chains from the beta ( $\beta$ ) globin group and two from the alpha ( $\alpha$ ) globin group. Each globin surrounds an iron-containing chemical group called a heme.



**Figure 11.2 Globin chain switching.** The subunit composition of human hemoglobin changes as the concentration of oxygen in the environment changes. With the switch from the placenta to the newborn's lungs to obtain oxygen, beta ( $\beta$ ) globin begins to replace gamma ( $\gamma$ ) globin.



**Figure 11.3 The pancreas is both an exocrine and an endocrine gland.** The expanded drawing shows the hormone-secreting pancreatic islets next to enzyme-secreting exocrine cells.

## Building Tissues and Organs

The globin chains affect one type of molecule, hemoglobin. Changing gene

expression and the resulting production of proteins can also be observed on a larger scale. For example, blood plasma contains about 40,000 different types of proteins. (Plasma is the liquid portion of

blood.) Ten types of proteins account for 90 percent of all the plasma protein molecules, and nearly half of those are one type, albumin. This means that many thousands of types of proteins are present in vanishingly small amounts, which is why only 300 or so of them have been described. But change the conditions—the person develops an infection or allergic reaction—and the protein profile of the plasma can change dramatically. Behind it all is differential gene expression.

Blood is a structurally simple tissue that is easy to obtain and study. A solid gland or organ, constructed from specialized cells and tissues, is much more complex. Its solid organization must be maintained throughout a lifetime of growth, repair, and changing external conditions.

Stem cell biology is shedding light on how genes are turned on and off during the development of an organ or gland. Researchers isolate individual stem cells and then see which combinations of growth factors, hormones, and other biochemicals must be added to steer development toward a particular cell type.

Consider the pancreas. It is a dual gland, with two types of cell clusters that have exocrine and endocrine functions (**figure 11.3**). An exocrine gland releases substances into ducts. The exocrine portion of the pancreas releases digestive enzymes, whereas an endocrine gland secretes directly into the bloodstream. The endocrine portion of the pancreas secretes polypeptide hormones that control nutrient use (**table 11.1**). The endocrine cell clusters are called pancreatic islets.

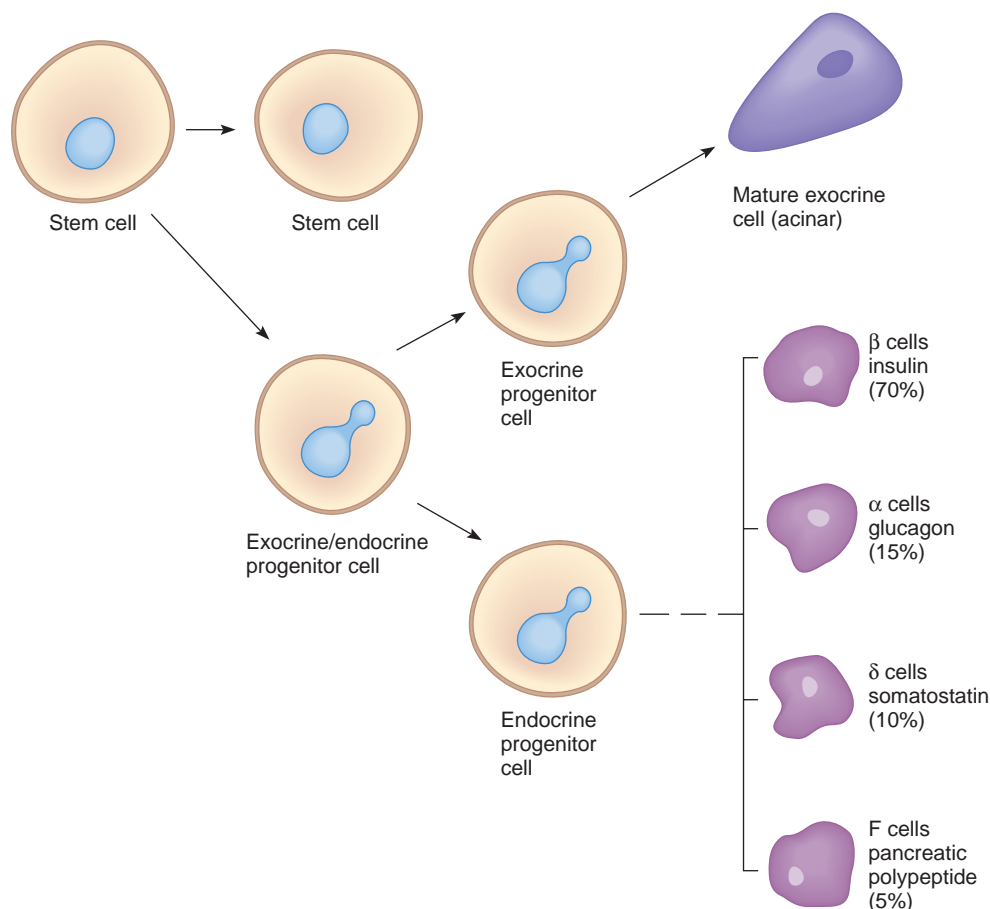
As the pancreas develops in the embryo, ducts form first. Within their walls reside rare stem cells and progenitor cells (see **figure 2.21**). Recall that a stem cell is an unspecialized cell that divides to yield another stem cell (self-renewal), and a progenitor cell that is partially specialized. When a transcription factor called *pdx-1* is activated, some of the progenitor cells divide. (Recall from chapter 10 that a transcription factor controls which genes are transcribed under certain conditions.) Some progenitor cells give rise to daughter cells that follow an exocrine pathway; they are destined to produce digestive enzymes



Table 11.1

## Pancreatic Hormones

Hormone	Function	Cell Type
Glucagon	Stimulates production of glucose	Alpha
Insulin	Stimulates cells to take up glucose	Beta
Somatostatin	Controls rate of carbohydrate absorption in blood	Delta
Pancreatic polypeptide	Controls secretion of digestive enzymes	F



**Figure 11.4 Building a pancreas.** A single type of stem cell theoretically gives rise to an exocrine/endocrine progenitor cell that in turn divides to yield more restricted progenitor cells that give rise to both mature exocrine and endocrine cells.

(figure 11.4). Other progenitor cells respond to different signals and divide to yield daughters that follow the endocrine pathway. The most familiar pancreatic hormone is insulin—its absence (or the

inability of cells to recognize it) causes diabetes mellitus.

Researchers can observe the specialization of pancreas cells by taking individual progenitor cells from human pancreas ducts

and supplying specific growth factors at particular times. This treatment stimulates certain progenitor cells to give rise to clusters that look and function like pancreatic islets. When exposed to glucose, the cells secrete insulin! If pancreatic stem cells can be isolated and cultured, it might be possible to coax a person with diabetes to produce new and functional pancreatic beta cells.

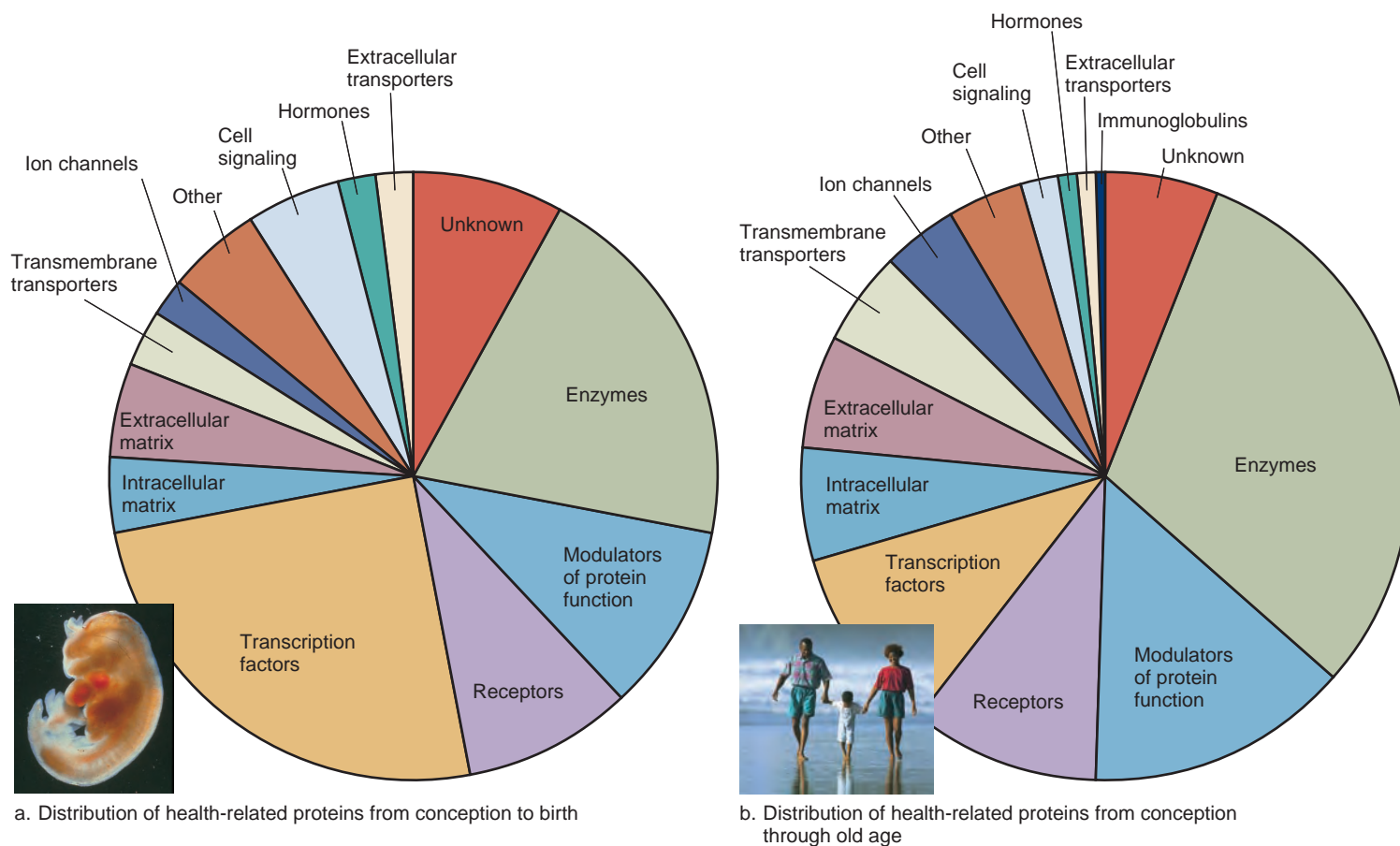
## Proteomics

A more complete portrait of gene expression emerges through **proteomics**, which considers all proteins made in a cell, tissue, gland, organ, or entire body. **Figure 11.5** depicts a global way of comparing the relative contributions of fourteen categories of proteins from conception through birth and from conception through old age.

The differences in proteins produced at different times make sense. For example, transcription factors are more abundant before birth because of the extensive cell differentiation of this period. During the prenatal period, enzymes are less abundant, perhaps because the fetus receives some enzymes through the placenta. Proteomic profiles shift with time and during periods of health and disease.

Another way to look at the proteome is by specific functions, which has led to the creation of various “ome” words. Genes whose encoded proteins control lipid synthesis constitute the “lipidome,” and those that monitor carbohydrate production and use form the “glycome.” “Omics” designations are helpful in sorting out the thousands of proteins a human cell can manufacture. However, identifying proteins is only a first step. The next hurdle is to determine how proteins with related functions interact—forming “interactomes.”

Gene expression profiles for different cell types under various conditions can provide valuable medical information. For example, 55 genes are overexpressed and 480 underexpressed in cells of a prostate cancer that has a very high likelihood of spreading—but not in a prostate cancer that will not spread. Altering gene expression has intriguing applications. For example, certain specialized cells can have their “stemness” genes reactivated and revert to functioning like stem cells.



**Figure 11.5 Proteomics meets medicine.** One way to analyze the effects of genes is to categorize them by the functions of their protein products, and then to chart the relative abundance of each class at different stages of development, in sickness and in health. The pie chart in **(a)** considers 14 categories of proteins that when abnormal or missing cause disease, and their relative abundance from conception to birth. The pie chart in **(b)** displays the same protein categories from conception to old age. These depictions represent just one of the many new ways of looking at differential gene expression.

## Key Concepts

1. Gene expression patterns change over time and in different cell types.
2. The subunit composition of hemoglobin changes in the embryo, fetus, and after birth.
3. As a pancreas forms, progenitor cells diverge from shared stem cells and their daughters specialize.
4. Proteomics tracks all of the proteins in a cell, tissue, organ, or organism under specific conditions.

## 11.2 Mechanisms of Gene Expression

We have already seen in a general sense how gene expression is controlled: signals instruct cells to activate combinations of

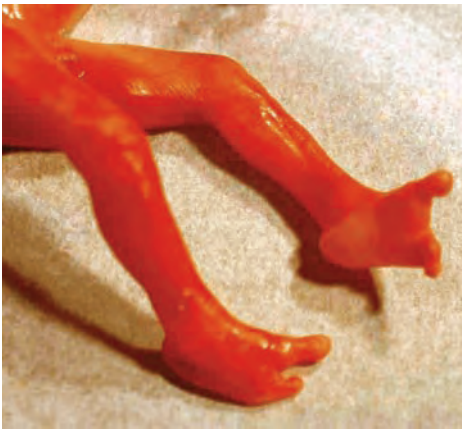
transcription factors, which control the genes that are transcribed. The transcription factors interact, positioning DNA to ease its interactions with yet other proteins.

Individuals may vary greatly in the degree to which a particular gene is expressed—that is, how much of a particular protein is made. Two factors that influence protein production are mutations in promoter sequences and the numbers of copies of a gene present in a person's genome.

Recall from chapter 10 that the promoter is a portion of the 5' end of a gene where RNA polymerase and transcription factors bind, marking the start point of transcription. Alterations in promoter sequences can change how readily or frequently transcription factors or RNA polymerase bind. This happens, for example, in a form of early-onset Alzheimer disease caused by mutation in the gene that encodes amyloid precursor

protein (APP) (OMIM 104760). A piece of APP, called amyloid beta peptide ( $A\beta$ ), corresponds to two exons and is the portion of the protein that accumulates in the brain. Most affected individuals have mutations in either of these two exons, but some people have mutations in the promoter of the APP gene, which causes  $A\beta$  to accumulate at twice the normal rate. An APP promoter mutation is a little like doubling a recipe simply by writing at the beginning “double the amount of the ingredients.”

People have differing numbers of copies of certain genes. The more copies, the more abundant the encoded protein in cells where the gene is transcribed. **Figure 11.6** shows an example of a condition associated with gene duplication, split hand–split foot malformation (OMIM 183600). Three genes that are involved in limb development are



**Figure 11.6 Split hand–split foot malformation may be caused by extra copies of three genes involved in hand and foot development.** Paradoxically, the extra genes do not yield extra digits but disturb the signals necessary for normal development. This is a stillborn.

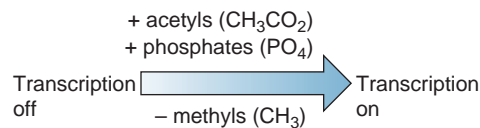
duplicated. The extra genes disrupt signaling in the embryo that controls elongation of skin outgrowths to form fingers and toes. So far more than 300 medical conditions have been associated with copy number variations. We revisit the impact of gene copy numbers in chapter 12.

We now look at two mechanisms that control gene expression: changing chromatin structure that regulates DNA accessibility, and small “interfering” RNA molecules that seek and destroy selected mRNA transcripts.

## Chromatin Remodeling

For many years, biologists thought that histone proteins were simple scaffolds that wind long DNA molecules into nucleosomes, little more than tiny spools (see figure 9.13). However, histones do much more: They play a major role in exposing DNA when and where it is to be transcribed, and shielding it when it is to be silenced. To do this, enzymes add or delete small organic chemical groups to histones in a process called **chromatin remodeling**. The resulting patterns of added chemical groups control the effect of histones on their associated protein-encoding genes.

The three major types of small molecules that bind to histones are acetyl groups, methyl groups, and phosphate groups (figure 11.7). The key to the role histones play

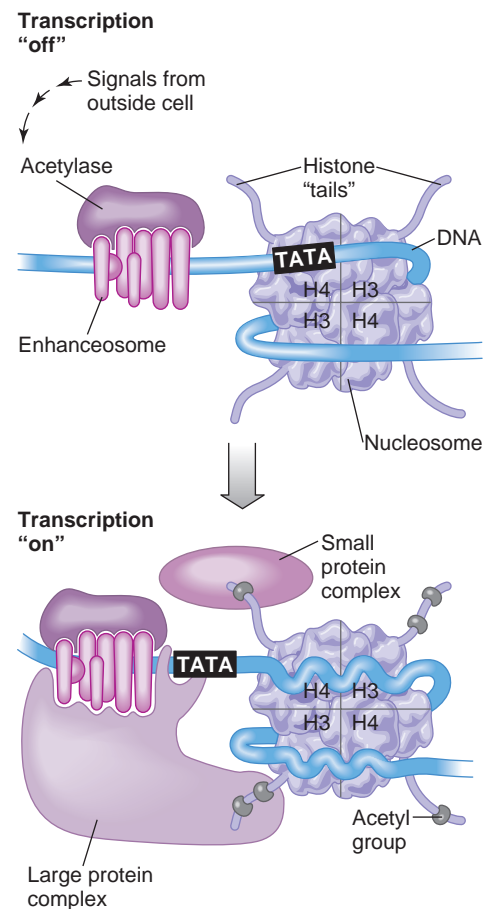


**Figure 11.7 Chromatin remodeling.** Chromatin remodeling adds or removes certain organic chemical groups to or from histones. The pattern of binding controls whether the DNA wrapped around the histones is transcribed or not.

in controlling gene expression lies in acetyl groups ( $\text{CH}_3\text{CO}_2$ ). At first, when acetyl groups were identified on the “tails” of certain histones, they were thought to loosen the grip between histones and genes by disrupting electrical attractions between the two. But when experiments revealed that the acetyls bind to very specific sites on certain histones, particularly to the amino acid lysine, the idea emerged that the pattern of histone binding in itself holds information, called the histone code.

For years the histone code was not much more than a controversial idea. Then, researchers at Columbia University deciphered the histone code for a particular gene—the one that encodes beta interferon, an immune system protein that combats viral infection. **Figure 11.8** shows how acetyl binding can subtly shift histone interactions in a way that eases transcription. A series of proteins moves the histone complex away from the TATA box, exposing it enough for RNA polymerase to bind and transcription to begin (see figure 10.7). First, a group of proteins called an enhanceosome attracts the enzyme (acetylase) that adds acetyl groups to specific lysines on specific histones. Then transcription factors bind, and transcription begins. Enzymes called deacetylases remove acetyl groups, which shuts off gene expression. Many researchers are now investigating whether the histone code for the beta interferon gene applies to other genes.

Methyl groups ( $\text{CH}_3$ ) are also added to or taken away from histones. Recall that in genomic imprinting (see figure 6.15), methyl groups silence DNA. When  $\text{CH}_3$  binds to a specific amino acid in a specific histone type, a protein called HP1 (for heterochromatin protein) is attracted, and shuts the DNA off. (Heterochromatin is dark-staining DNA, and is discussed further in chapter 13.)  $\text{CH}_3$  groups are added, and methylation spreads



**Figure 11.8 Acetylated histones allow transcription to begin.** Once acetyl groups are added to particular amino acids in the tails of certain histones, the TATA box becomes accessible to transcription factors. In this case, transcription of the beta interferon gene can begin. (H3 and H4 are histone types.)

from the tail of one histone to the adjacent histone, propagating the gene silencing.

The modified state of chromatin can be passed on when DNA replicates. These changes are heritable, but they do not directly affect the DNA sequence—that is, they are epigenetic. Effects of methylation can sometimes be seen when MZ (identical) twins inherit the same disease-causing genotype, but only one twin is sick. The reason for the discordance may be different patterns of methylation of the gene.

Enzymes that add or delete acetyl, methyl, and phosphate groups must be in a balance that controls which genes are expressed and which are silenced. One limitation to altering chromatin remodeling to treat inherited disease is that this action



Table 11.2

## Disorders of Chromatin Remodeling

Disease	OMIM	Protein	Symptoms	Defect
$\alpha$ -thalassemia mental retardation syndrome	301040	ATRX	Anemia, mental retardation	Undermethylation of heterochromatin
ICF syndrome	242860	DNMT3B	Immunodeficiency, unstable centromeres, facial anomalies	Undermethylation of repeats
Rett syndrome	312750	MECP2	Repetitive movements, irregular breathing, seizures, loss of motor control, profound neurodegeneration starting at 6 months	Failure to remove acetyls from histones on gene <i>DLX5</i> expressed in brain
Rubinstein-Taybi syndrome	180849	CBP	Mental retardation, short stature, facial anomalies	Adds acetyl groups to certain histones, causing inappropriate transcription of some genes

could affect the expression of many genes—not just the one implicated in the disease. **Table 11.2** lists disorders that result from abnormal chromatin remodeling.

## RNA Interference

Genetics continues to surprise us. Although usually only one strand of DNA is transcribed, up to 8 percent of genes may be transcribed from both strands, leading to a phenomenon called **RNA interference** (RNAi) that destroys specific mRNA molecules. For some genes, the sequence is such that transcripts can complementary base pair within themselves, folding up into short, double-stranded sections termed hairpin loops. When complementary DNA strands are transcribed and a hairpin loop forms, certain proteins trim the hairpin, creating a “small interfering RNA,” known as a siRNA (**figure 11.9**). Such an RNA opens, finds, and binds its mRNA complement, tagging it for dismantling by

enzymes. In this way, an siRNA silences its complement.

Small siRNAs in the cytoplasm bind mature mRNAs after transcription ends. RNA interference is not the normal dismantling of a used mRNA, but a distinct mechanism that suppresses the expression of certain genes. Some siRNAs act in the nucleus, where they add methyls to histones, shutting off transcription at its start.

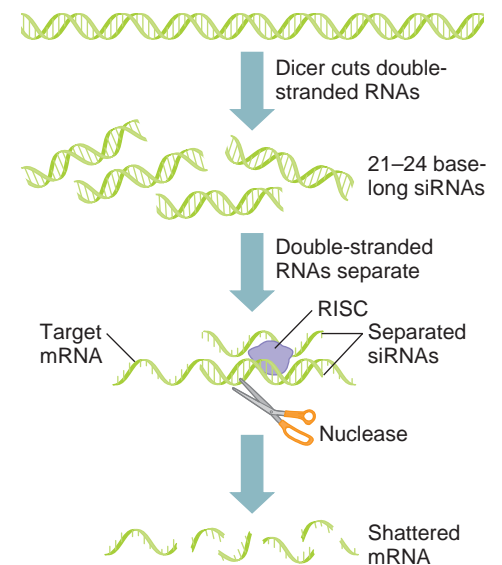
Several proteins and protein complexes orchestrate RNA interference (**figure 11.10**). An enzyme called dicer first cuts long double-stranded RNAs into 21- to 24-base-long pieces. Then a large protein complex called RISC (for RNA-induced silencing complex) binds the pieces and unwinds them, exposing single strands. The antisense RNA strands—so-called because they are complementary to the targeted RNA—then attract the mRNAs, which are chewed up by enzymes (nucleases) that are part of RISC.

RNAi is seen in all eukaryotic organisms (those whose cells have nuclei). Its function is probably to rid a genome of viral or

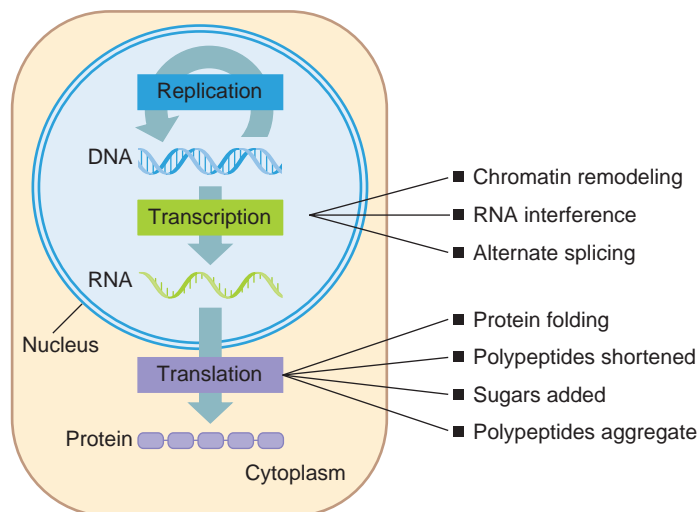
other foreign DNA. Even though we do not yet fully understand the phenomenon, the discovery of RNAi has spawned a new biotechnology, in which researchers synthesize short RNAs to intentionally destroy particular mRNAs, “knocking down” gene expression. This approach can be used to discover the functions of specific genes, or to silence dangerous ones. For example, experimental



**Figure 11.9** RNA hydrogen bonds with itself, forming hairpin loops.



**Figure 11.10 RNA interference.** Dicer cuts double-stranded portions of RNA molecules, which then associate with RNA-induced silencing complexes (RISCs). The RNAs open, revealing single strands that locate and bind specific mRNAs. Nucleases then break down the targeted mRNAs.



**Figure 11.11 A summary of the events of gene expression.** At the level of transcription, chromatin remodeling determines which genes are transcribed, RNA interference removes certain mRNA molecules, and alternate splicing creates different forms of a protein by combining exons in different ways. At the level of translation, a protein must fold a certain way. Certain polypeptides must be shortened, attached to sugars, or aggregated.

vaccines using RNAi “knock-down” (deplete) expression of key genes in the viruses that cause SARS, AIDS, polio, and hepatitis C. To treat cancer, siRNAs might knock down genes whose protein products destabilize the cell cycle. In agriculture, siRNAs can knock down an enzyme required for caffeine synthesis in coffee plants, creating a better-tasting decaf. RNAi has also been used to knock down a toxin, called gossypol, found in the cotton plant, making it possible to eat the very abundant seed. The naturally occurring gossypol makes the seed toxic.

**Figure 11.11** summarizes the processes and modifications that affect gene expression.

### 11.3 Proteins Outnumber Genes

When the human genome project began in 1986, researchers expected to find 100,000 or more genes. Although they eventually cataloged only 20,600 or so genes, these genes encode 200,000 or more proteins. But this apparent paradox of a few genes specifying many proteins wasn’t entirely unexpected. The “genes in pieces” pattern of exons and introns, discovered in the mid-1970s, had suggested that this might be the case. The scattered architecture of

the human genome is a little like using a few items of clothing to assemble many outfits by combining them in different ways.

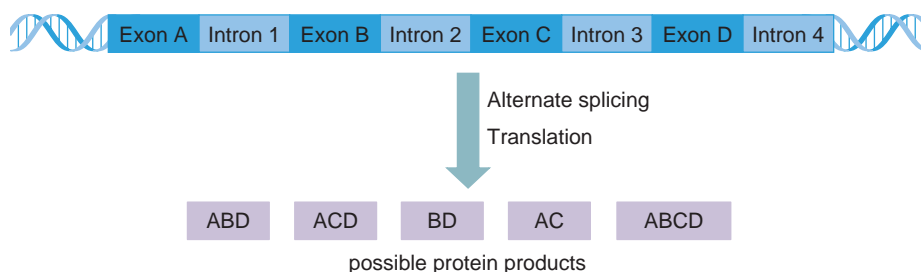
The discovery of introns in 1977 first raised the possibility that some genes could specify more than one protein by mixing and matching exons through alternate splicing (**figure 11.12**). It might be advantageous to do this in different tissues or under different circumstances. For example, an antibody-secreting cell of the immune system at first produces a shortened version of the antibody that is presented on the cell’s surface, which alerts other cells. As the infection progresses, the cell transcribes a different exon that adds a portion to the antibody that enables it to be secreted into the bloodstream, where it attacks the pathogen.

Alternate splicing explains how a long sequence of DNA can specify more mRNAs than genes. On a part of chromosome 22, for example, 245 genes yield 642 mRNA transcripts. About half of all human genes are alternately spliced.

Introns present another way to maximize the protein-encoding information content of DNA. Introns may seem wasteful, little more than vast stretches of DNA bases that outnumber and outsize exons. But a DNA sequence that is an intron in one context may encode protein in another. Consider prostate specific antigen (PSA), a protein found on certain cell surfaces that is overproduced in some prostate cancers. The gene for PSA has five exons and four introns. However, it is alternately spliced to encode a different protein, called PSA-linked molecule (PSA-LM), that consists of the first exon

#### Key Concepts

1. Acetyl, phosphate, and methyl groups bind to histone proteins, controlling transcription.
2. Acetyl and phosphate groups turn on transcription; methyl groups turn it off.
3. The patterns of histones that activate a particular gene may follow rules like a code.
4. In RNA interference, short double-stranded RNAs separate, and the antisense strands bind specific mRNAs, marking them for destruction.



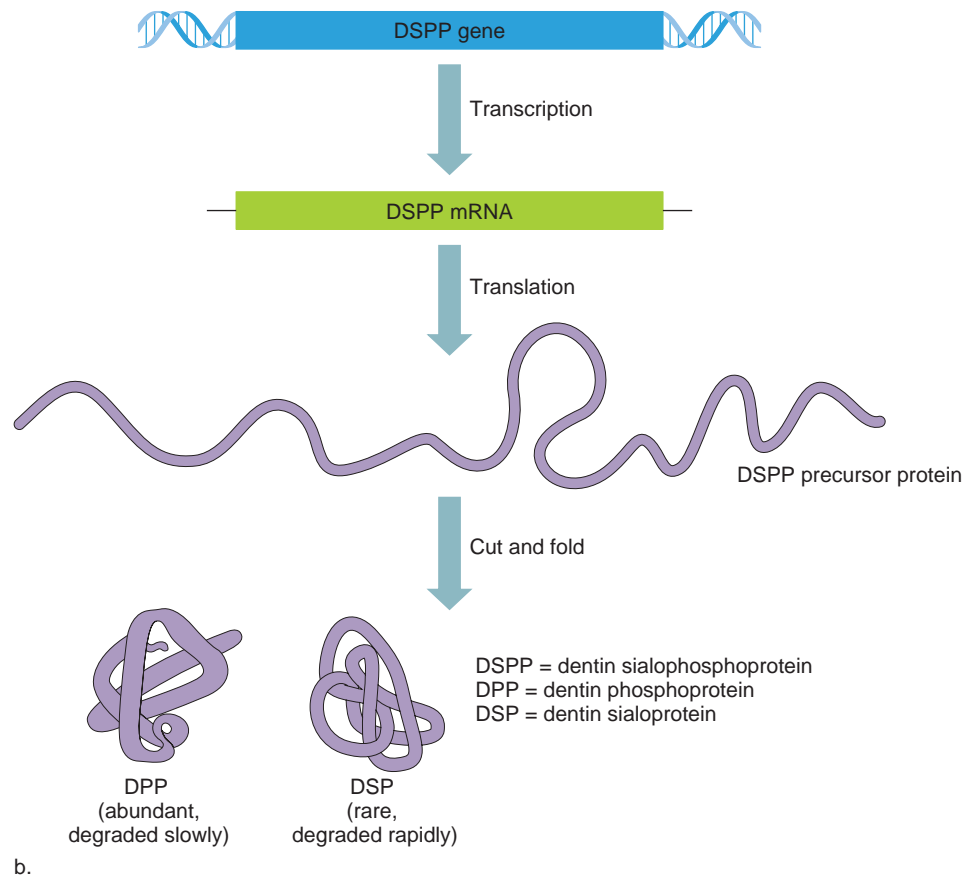
**Figure 11.12 Exons provide flexibility in gene structure that expands gene number.** Alternate splicing enables a cell to manufacture different versions of a protein by adding or deleting parts. Introns are removed and exons retained.



a.

### Figure 11.13 Another way to encode two genes in one.

(a) The misshapen, discolored, and enamel-stripped teeth of a person with dentinogenesis imperfecta were at first associated with deficiency of the protein DPP. Then researchers discovered that DSP is deficient, too, but is usually present in such small amounts that its role wasn't recognized. (b) Both DPP and DSP are cut from the same larger protein, but DSP is degraded faster.



and the fourth intron. The two proteins (PSA and PSA-LM) seem to work against each other. When the level of one is high, the other is low. New blood tests may consider levels of both proteins to more accurately assess the risk of developing prostate cancer.

In another situation where introns may account for the overabundance of proteins compared to genes, a DNA sequence that is an intron in one gene's template strand may encode protein on the coding strand. This is the case for the gene for neurofibromin, which when mutant causes neurofibromatosis type 1, an autosomal dominant condition that causes benign tumors beneath the skin and "café au lait" spots on the skin surface. Within an intron of the neurofibromin gene, but on the coding strand, are instructions for three other genes.

Still another way a gene can maximize its informational content is for its encoded protein to be cut to yield two products. This happens in dentinogenesis imperfecta (OMIM 125490), which is an autosomal

dominant condition that causes discolored, misshapen teeth with peeling enamel (figure 11.13). The dentin, which is the bonelike substance beneath the enamel that forms the bulk of the tooth, is abnormal. Dentin is a complex mixture of extracellular matrix proteins. Dentin protein is 90 percent collagen, and this and most of the rest of the proteins are also found in bone. However, two proteins are unique to dentin: dentin phosphoprotein (DPP) and dentin sialoprotein (DSP). A single gene encodes these two proteins.

Researchers had associated abnormal DPP with dentinogenesis imperfecta. However, DPP, because it is much more abundant than DSP, may have overshadowed the rarer protein. Both DPP and DSP are translated from a single mRNA molecule as the precursor protein dentin sialophosphoprotein (DSPP). DPP may be much more abundant because it is longer-lived than DSP; that is, DSP is degraded faster.

Table 11.3 summarizes mechanisms that maximize genomic information.

Table 11.3

### Maximizing the Informational Content of Genes

Mechanism	Example
Alternate splicing	antibody-producing cell
Use of introns	PSA and PSA-LM; NF1
Two proteins split from precursor	Dentinogenesis imperfecta

### Key Concepts

1. Only a tiny proportion of the genome encodes protein, yet the number of proteins greatly outnumbers known protein-encoding genes.
2. Alternate splicing, introns that encode protein, and cutting a precursor protein maximize the number of proteins that DNA encodes.



11.4 Most of the Human Genome Does Not Encode Protein

When the first molecular geneticists worked out the details of transcription and translation in the 1960s, they never imagined that only 1.5 percent of human DNA encodes protein. What does the “other” 98.5 percent do? It includes viral sequences, sequences that encode RNAs other than mRNA (called noncoding or ncRNAs), introns, promoters and other control sequences, and repeated sequences (table 11.4). Most of the genome is transcribed—it isn’t “junk.”

Viral DNA

Our genomes also include DNA sequences that represent viruses. Viruses are nonliving infectious particles that consist of a nucleic acid (DNA or RNA) encased in a coat built of proteins. A virus replicates by commandeering a cell, taking over its transcriptional and translational machinery to mass-produce viruses, which exit the cell. Sometimes the viral nucleic acid remains in a chromosome of a host cell. A DNA virus may do so directly; an RNA virus first uses an enzyme (reverse transcriptase) to copy its genetic material into DNA, which then inserts into a host chromosome.

About 100,000 sequences in our DNA, of varying length and comprising about 8 percent of the human genome, were once a type of RNA virus called a retrovirus. The name refers to their direction of genetic information transfer, which is opposite the DNA to RNA to protein route. Retroviral sequences lodged in chromosomes are termed endogenous because they are carried from generation to generation of the host; those in our own chromosomes are called human endogenous retroviruses, or HERVs.

By comparing HERV sequences to similar viruses in other primates, researchers have traced HERVs to a sequence representing a virus that infected our ancestors’ genomes about five million years ago. Since then, HERV sequences have exchanged parts (recombined) and mutated to the extent that they no longer make us sick—yet they retain the theoretical ability to do so. Further recombination and mutation

Table 11.4 Some Nonprotein-Encoding Parts of the Human Genome	
	Function or Characteristic
Viral DNA	Evidence of past infection
Noncoding RNA genes	
tRNA genes	Connect mRNA codon to amino acid
rRNA genes	Parts of ribosomes
Pseudogenes	DNA sequences very similar to known genes that are not translated
Small nucleolar RNAs	Process rRNA in nucleolus
Small nuclear RNAs	Parts of spliceosomes
Telomerase RNA	Adds bases to chromosome tips
Xist RNA	Inactivates one X chromosome in cells of females
Introns	Parts of genes that are cut out of mRNA
Promoters and other control sequences	Guide enzymes that carry out DNA replication, transcription, or translation
Small interfering RNAs	Control transcription
Micro RNAs	Control transcription of many genes
Repeats	
Transposons	Repeats that move around the genome
Telomeres	Chromosome tips that control the cell cycle
Centromeres	Largest constriction in a chromosome, providing attachment points for spindle fibers
Duplications of 10 to 300 kilobases	Unknown
Simple short repeats	Unknown

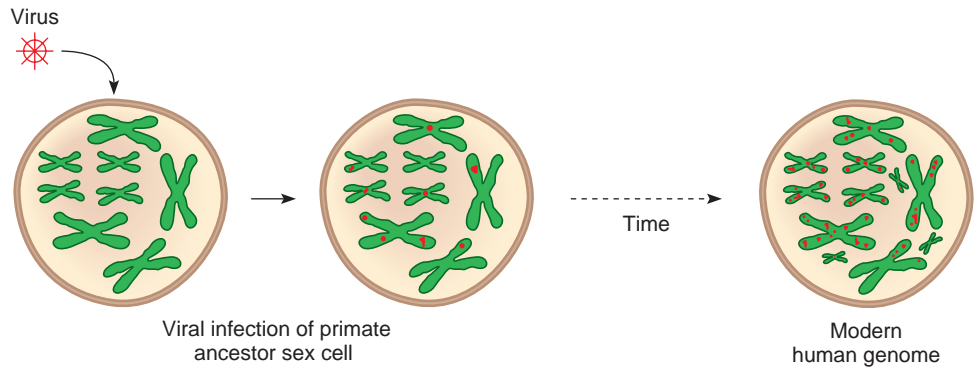


Figure 11.14 The human genome includes viral DNA sequences. Most if not all of them do not harm us.

could take them in an infectious direction. In fact, researchers have combined parts of HERVs and regenerated an ancient, infectious HERV. They named it Phoenix, after the legendary bird that arose from the

ashes. Harmless HERVs are passed from human generation to generation because they are parts of our chromosomes. They tend to increase in number with time, as figure 11.14 shows.

## Noncoding RNAs

At least a third of the human genome is transcribed into RNA types other than mRNA, such as tRNA and rRNA. The rate of transcription of a cell's tRNA genes is attuned to cell specialization. The proteins of a skeletal muscle cell, for example, would require different amounts of certain amino acids than the proteins of a white blood cell, and therefore different amounts of the corresponding tRNAs, too.

Human tRNA genes are dispersed among the chromosomes in clusters—25 percent of them are on the sixth-largest chromosome, for example. Altogether, our 500 or so types of tRNA genes account for 0.1 percent of the genome.

The 243 types of rRNA genes are grouped on six chromosomes, each cluster harboring 150 to 200 copies of a 44,000-base repeat sequence. Once transcribed from these clustered genes, the rRNAs go to the nucleolus, where yet another type of ncRNA called small nucleolar RNA (snoRNA) cuts them into their final forms.

Hundreds of thousands of ncRNAs are neither tRNA nor rRNA, nor snoRNAs, nor the other less abundant types described in table 11.4. Instead, they are transcribed from DNA sequences called **pseudogenes**. A pseudogene is very similar in sequence to a particular protein-encoding gene, and it may be transcribed into RNA, but it is not translated into protein. Presumably it is altered in sequence from an ancestral gene in a way that impairs its translation—perhaps the encoded amino acids cannot

fold into a functional protein. Pseudogenes may be remnants of genes past, variants that diverged from the normal sequence too greatly to encode a working protein. Pseudogenes are incredibly common in the human genome. Our tRNA genes alone have more than 324 pseudogenes.

## Repeats

The human genome is riddled with highly repetitive sequences that may be a different type of information than a protein's amino acid sequence. Perhaps repeat size or number constitute another type of molecular language. Or, perhaps some types of repeats help to hold a chromosome together.

The most abundant type of repeat is a sequence of DNA that can jump about the genome. It is called a transposable element, or **transposon** for short. Geneticist Barbara McClintock originally identified transposons in corn in the 1940s, and they were rediscovered in bacteria in the 1960s. Transposons comprise about 45 percent of the human genome sequence, and typically repeat in many copies. Some transposons include parts that encode enzymes that cut them out of one chromosomal site and integrate them into another. Transposons are classified into four groups: by size, whether they are transcribed into RNA, which enzymes they use to move, and whether they resemble bacterial transposons.

An example of a specific type of repeat is Alu. Each Alu repeat is about 300 bases long, and a human genome may contain 300,000 to 500,000 of them. Alu repeats

comprise 2 to 3 percent of the genome, and they have been increasing in number over time because they can copy themselves. We don't know exactly what these common repeats do, if anything. They may serve as attachment points for proteins that bind newly replicated DNA to parental strands before anaphase of mitosis, when replicated chromosomes pull apart.

Rarer classes of repeats include those that comprise telomeres, centromeres, and rRNA gene clusters; duplications of 10,000 to 300,000 bases (10 to 300 kilobases); copies of pseudogenes; and simple repeats of one, two, or three bases. In fact, the entire human genome may have duplicated once or even twice, as is discussed further in chapter 16.

Our understanding of the functions of repeats lags far behind our knowledge of the roles of the various noncoding RNA genes. Repeats may make sense in light of evolution, past and future. Pseudogenes are likely vestiges of genes that functioned in our nonhuman ancestors. Perhaps the repeats that seem to have no obvious function today will serve as raw material from which future genes may arise.

## Key Concepts

1. Most of the genome encodes many types of RNA as well as viral sequences, introns, promoters, and other control sequences and repeats.
2. We do not know the functions of some repeats.

## Summary

### 11.1 Gene Expression Through Time and Tissue

1. Changes in gene expression occur over time at the molecular level (globin switching), at the tissue level (blood plasma), and at the organ/gland level (pancreas development). We can track expression changes in individual genes or use DNA microarrays to envision expression patterns of many genes at a time.
2. **Proteomics** catalogs the types of proteins in particular cells, tissues, organs, or entire organisms under specified conditions.

### 11.2 Mechanisms of Gene Expression

3. The pattern of chemical groups on histones forms an epigenetic code that spreads, can be transmitted when the cell divides, and controls gene expression.
4. Acetylation of certain histones enables the transcription of associated genes. Phosphorylation and methylation are also important in **chromatin remodeling**.
5. **RNA interference** silences genes in the nucleus and removes certain mRNAs in the cytoplasm.

### 11.3 Proteins Outnumber Genes

6. Only 1.5 percent of the human genome encodes protein, yet those 20,600 or so genes specify up to 200,000 proteins.
7. Mechanisms to explain the mismatch between gene and protein diversity include alternate splicing, use of introns, and cutting proteins translated from a single gene.

### 11.4 Most of the Human Genome Does Not Encode Protein

8. The rest of the genome includes viral sequences, noncoding RNAs, introns, promoters and other controls, and repeats.

# Review Questions

1. Why is control of gene expression necessary?
2. Describe three types of cells and how they differ in gene expression.
3. Explain how a mutation in a promoter can alter gene function.
4. What is the environmental signal that stimulates globin switching?
5. How does development of the pancreas illustrate differential gene expression?
6. Distinguish between a genetic and an epigenetic change. What do they have in common? How do they differ?
7. How do histones control gene expression, yet genes also control histones?
8. Name two types of chemical reactions that silence transcription.
9. What controls whether histones allow DNA wrapped around them to be transcribed?
10. What information is needed to use RNAi to treat a viral infection?
11. How does alternate splicing generate more than one type of protein from the information in a gene?
12. The media often call DNA sequences that do not encode protein “junk.” Give three reasons why this DNA should not be considered junk.
13. In the 1960s, a gene was defined as a continuous sequence of DNA, located permanently at one place on a chromosome, that specifies a sequence of amino acids from one strand. List three ways this definition has changed.
14. Give three examples of discoveries mentioned in the chapter that changed the way we think about the genome.
15. How can one of the two dental proteins implicated in dentinogenesis imperfecta be much more abundant than the other if they are both transcribed and translated from the same gene?
16. State four roles of DNA other than encoding protein.

# Applied Questions

1. Invent a new “omics” to investigate genes that are functionally related in a particular way.
  2. Drug companies are synthesizing compounds that inhibit the enzymes that either put acetyl groups on histones or take them off. Would a drug that combats a cancer caused by too little expression of a gene that normally suppresses cell division add or remove acetyl groups?
  3. Chromosome 7 has 863 protein-encoding genes, but many more proteins. The average gene is 69,877 bases, but the average mRNA is 2,639 bases. Explain both of these observations.
  4. CHARGE syndrome (OMIM 214800) causes heart defects, visual problems, facial palsy, blocked nostrils, and difficulty swallowing. A mutation in a gene called *Chd1* causes the condition. The protein product of this gene recognizes and binds methyl groups on certain histones. Explain how this mutation leads to pleiotropy (multiple symptoms).
  5. In chronic myelogenous leukemia, an exchange between two nonhomologous chromosomes fuses two genes. Expression of the fused gene increases the rate of synthesis of tyrosine kinase, which lifts control of the cell cycle. How might RNA interference be used to treat this cancer?
  6. Which is a more targeted approach to treating cancer, removing methyl groups to reactivate genes that normally suppress cancer, or using RNAi?
  7. How many different proteins encompassing two exons can be produced from a gene that has three exons?
  8. When researchers compared the number of mRNA transcripts that correspond to a part of chromosome 19 to the number of protein-encoding genes in the region, they found 1,859 transcripts and 544 genes. Account for the discrepancy.
  9. Many people with trisomy 21 Down syndrome (an extra chromosome 21; see section 13.3) who survive into adulthood develop early-onset Alzheimer disease. The APP gene which when mutant causes this form of Alzheimer disease is on chromosome 21. Explain how this form of Alzheimer disease in trisomy 21 individuals differs from the same disorder caused by a mutation in the APP promoter in a person who has the normal two copies of chromosome 21.
- Web Activities**  
Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, Chapter 11**,

and **Web Activities** to find the website links needed to complete the following activities.

10. Many companies are offering products based on RNA interference to use in research to “knock down” gene expression. Go to one of the following websites for the following companies, or find others. Research a particular RNAi product, and suggest how it might be used. (The companies listed have all existed for many years. There are many newer ones.)

Ambion

Invitrogen

New England Biolabs

Novagen

Qiagen

Stratagene

## Case Studies

11. Jerrold is 38 years old. His body produces too much of the hormone estrogen and as a result, he has enlarged breasts. He had a growth spurt and developed pubic hair by age 5, and then his growth dramatically slowed so that his adult height is well below normal. He has a very high-pitched voice and no facial hair, which reflect the excess estrogen. Jerrold’s son, Timmy, is 8 years old and has the same symptoms.



Jerrold and Timmy have an overactive gene for aromatase, an enzyme required to synthesize estrogen. Five promoters control expression of the gene in different tissues, and each promoter is activated by a different combination of hormonal signals. The five promoters lead to estrogen production in skin, fat, brain, gonads (ovaries and testes) and placenta. In premenopausal women, the ovary-specific promoter is highly active, and estrogen is abundant. In men and postmenopausal women, however, only small amounts of

estrogen are normally produced, in skin and fat. The father and son have a wild type aromatase gene, but high levels of estrogen in several tissues, particularly fat, skin, and blood. They do, however, have a mutation that turns around an adjacent gene so that the aromatase gene falls under the control of a different promoter. Suggest how this phenotype arises.

12. Margaret is 102 years old, and she still walks at least half a mile a day, albeit slowly. She is a trim vegetarian who has

rarely been ill her entire life. Morris is an obese, balding 62-year-old man who has high blood pressure and colon cancer. How might their proteome portraits, such as the one in figure 11.5, differ? (Hint: Reread Reading 3.1, The Centenarian Genome.)

## A Second Look

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1. Why didn't more children with ALL respond to chemotherapy drugs?
2. Why does it make more sense to use DNA microarray gene expression data to choose a drug to treat leukemia than to base the decision on symptoms or the appearance of the cancerous cells?
3. Which type of characteristic do you think should be used to define leukemias? Cite a reason for your choice.

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# Gene Mutation

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## TWO MUTATIONS STRIKE ONE GENE—AND ONE LITTLE GIRL

Newborn screening for sickle cell disease indicated that Juanita was a carrier, like her father. Unlike most carriers, though, Juanita was sick. She was hospitalized a few times for an enlarged spleen and anemia, and some of her red blood cells were sickled.

Juanita ran into trouble at 19 months of age, on a plane. Midflight, she suddenly became ill, her spleen swelling enormously and her blood pressure plummeting. When Juanita turned blue, a doctor on the flight administered oxygen. The child safely reached a hospital, where her spleen was removed. She had severe hemolytic anemia—her cells were sickling *and* bursting. This double danger hinted at the cause of Juanita's problem: she had two mutations in a beta globin gene.

The mutation Juanita inherited from her father changed the sixth amino acid in the beta globin gene from glutamic acid to valine, but a second mutation affected another part of the encoded protein. Since her father's gene did not have the second mutation, it must have occurred in the sperm that was to join an ovum to become, eventually, Juanita. The second mutation changed the 68th amino acid in beta globin from leucine to phenylalanine. This change exposed part of the molecule that is normally shielded, destabilizing the entire globin molecule. Although Juanita's mother contributed a normal allele, the overall effect in the double-carrier child was a drastic lowering of the attraction of oxygen to hemoglobin. However, this happens only in the presence of a particular metabolic by-product made in the spleen only at high altitude—such as aboard a jet.



a.



b.

Normal red blood cells (*top*) are concave discs; sickled red blood cells (*bottom*) look very different. Several mutations can cause red blood cells to sickle. The abnormal cells block circulation where and when oxygen levels fall, causing great pain.



A **mutation** is a change in a DNA sequence that is present in less than 1 percent of individuals in a population. Mutation can occur at the DNA level, substituting one DNA base for another or adding or deleting a few bases, or at the chromosome level, the subject of chapter 13. This chapter discusses mutations at the DNA level.

Mutation can affect any part of genome, including sequences that encode proteins or control transcription; in introns; repeats; and sites critical to intron removal and exon splicing. However, not all DNA sequences are equally likely to mutate.

The effects of mutation vary. A mutation can stop or slow production of a protein, overproduce it, or impair the protein's function—such as altering its secretion, location, or interaction with another protein. Geneticists often describe the effect of a mutation as a “loss of function” when the gene's product is reduced or absent, or as a “gain of function” when the gene's action changes in some way. Most mutations are recessive and cause a loss of function. Gain-of-function mutations tend to be dominant.

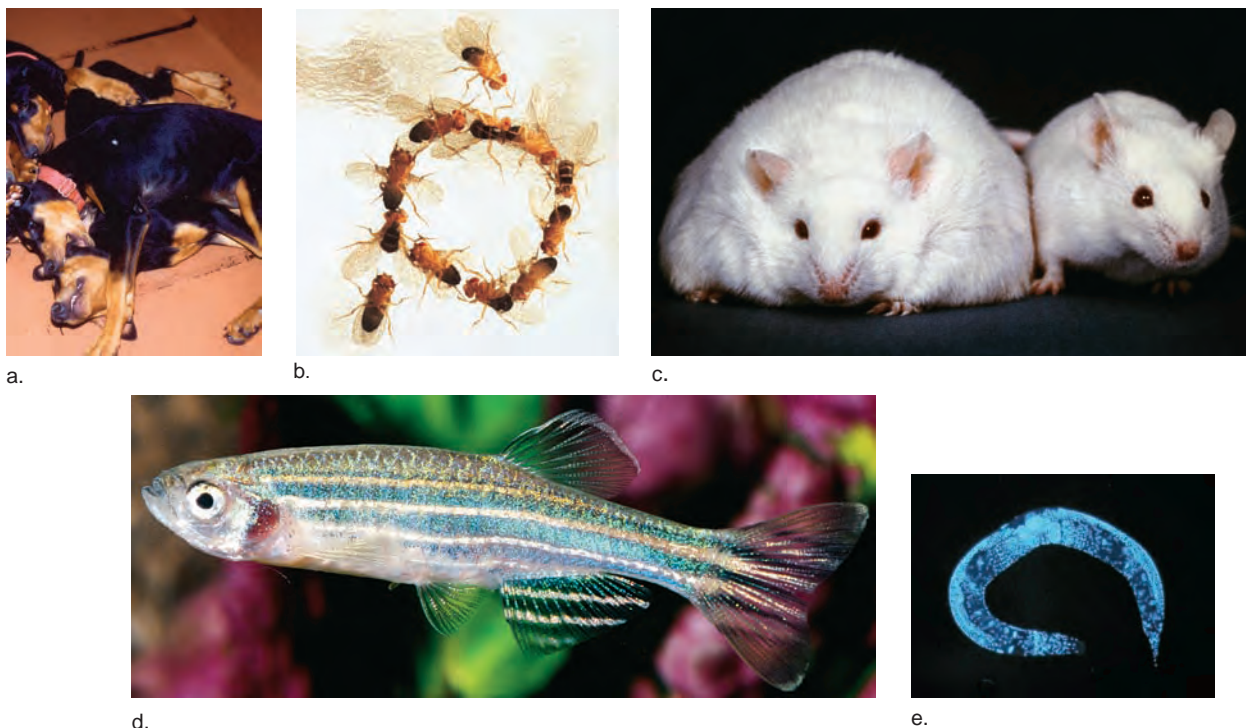
The terms *mutation* and *polymorphism* can be confusing, because both denote a genetic change. Recall from chapter 7 that a single nucleotide polymorphism, or SNP, is a single base change. So are many mutations. The distinction between mutation and polymorphism is largely artificial. Geneticists define a mutation as being present in less than 1 percent of a population and a polymorphism as being present in more than 1 percent of a population. The consequences of this distinction provide the logic underlying the more popular view that a mutation is “bad” but a polymorphism is a “harmless variant.” That is, if a genetic change greatly impairs health, individuals with it are unlikely to reproduce, and the mutant allele remains uncommon. (Chapter 15 explains why it doesn't actually disappear.) A polymorphism that does not harm health, or is even beneficial, will remain prevalent in a population or even increase in frequency. This chapter deals mostly with mutations that alter the phenotype.

Not all mutations are harmful. For example, a mutation protects against HIV infection. About 1 percent of the general population is homozygous for a recessive

allele that encodes a cell surface protein called CCR5 (see figure 17.15). To infect an immune system cell, HIV must bind CCR5 and another protein. Because the mutation prevents CCR5 from moving to the cell surface, HIV cannot bind. Heterozygotes are partially protected against HIV infection.

The term *mutation* refers to genotype—that is, a change at the DNA or chromosome level. The familiar term **mutant** refers to an unusual phenotype. The nature of a mutant phenotype depends upon how the mutation affects the gene's product or activity, and usually connotes an abnormal or unusual characteristic. However, a mutant phenotype may also be an unusual variant that is nevertheless “normal,” such as red hair.

In an evolutionary sense, mutation has been essential to life, because it produces individuals with variant phenotypes who are better able to survive specific environmental challenges, including illnesses. Our evolutionary relatedness to other species enables us to study many mutations in non-human species, which can provide information on our own. **Figure 12.1** introduces some model organisms used in experiments



**Figure 12.1** Model organisms can teach us about ourselves, thanks to genetic similarities. (a) The human gene for narcolepsy was discovered with the help of sleeping dogs. (b) Homosexuality is studied using male fruit flies that display mating behavior toward each other. (c) Obese mice led to the discovery of the gene leptin, which influences body weight. (d) Zebrafish have short generation times and transparent embryos enabling researchers to observe organ development. (e) The tiny roundworm *Caenorhabditis elegans* has been a favorite in studies of development because the fate of every single one of its cells has been meticulously traced.

and research, some of whom we have met in previous chapters.

A mutation may be present in all the cells of an individual or just in some cells. In a **germline mutation**, the change occurs during the DNA replication that precedes *meiosis*. The resulting gamete and all the cells that descend from it after fertilization have the mutation—that is, every cell in the body. In contrast, a **somatic mutation** happens during DNA replication before a *mitotic* cell division. All the cells that descend from the original changed cell are altered, but they might only comprise a small part of the body. Somatic mutations are responsible for certain cancers (see Reading 18.1 and figure 18.5).

## 12.1 Mutations Can Alter Proteins—Three Examples

Identifying how a mutation causes symptoms has clinical applications, and also reveals the workings of biology. Following are three examples of mutations that cause disease.

### The Beta Globin Gene Revisited

The first genetic illness to be understood at the molecular level was sickle cell disease (figure 12.2). In 1904, young medical intern Ernest Irons noted “many pear-shaped and elongated forms” in a blood sample from a

dental student in Chicago who had anemia. Irons sketched this first view of sickle cell disease at the cellular level, and reported his findings to his supervisor, physician James Herrick. Alas, Herrick published the work but did not mention Irons. Herrick has been credited with the discovery ever since.

In 1949, Linus Pauling discovered that hemoglobin from healthy people and from people with the anemia, when placed in a solution in an electrically charged field (a technique called electrophoresis), moved to different positions. Hemoglobin from the parents of people with the anemia, who were carriers, moved to both positions.

The difference between the two types of hemoglobin lay in beta globin. Recall from figure 11.1 that adult hemoglobin consists of two alpha polypeptide subunits and two beta subunits. Protein chemist V. M. Ingram took a shortcut to localize the mutation in the 146-amino-acid-long protein. He cut normal and sickle hemoglobin with a protein-digesting enzyme, separated the pieces, stained them, and displayed them on filter paper. The patterns of fragments—known as peptide fingerprints—were different for the two types of hemoglobin. This meant, Ingram deduced, that the two molecules differ in amino acid sequence. Then he homed in on the difference. One piece of the molecule in the fingerprint, fragment four, occupied a different position in each of the two types of hemoglobin. Because this peptide was only 8 amino acids long, Ingram needed to decipher only that short sequence to find the site of the mutation. It was a little like knowing which sentence on a page contains a typographical error.

Ingram identified the tiny mutation responsible for sickle cell disease: a substitution of the amino acid valine for the glutamic acid that is normally the sixth amino acid in the beta globin polypeptide chain. At the DNA level, the change was even smaller—a CTC to a

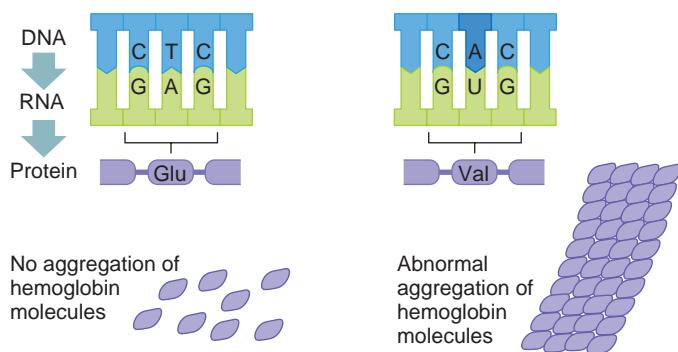
CAC, corresponding to RNA codons GAG and GUG. This was learned after researchers deciphered the genetic code. The valine at this position changes the surfaces of hemoglobin molecules so that in low-oxygen conditions they attach at many more points than they would if the wild type glutamic

acid were at the site. The aggregated hemoglobin molecules form ropelike cables that bend red blood cells into rigid, fragile, sickle-shaped structures. The misshapen cells lodge in narrow blood vessels, cutting off local blood supplies. Once a blockage occurs, sickling speeds up and spreads, as the oxygen level falls. The result is great pain in the blocked body parts, particularly the hands, feet, and intestines. The bones ache, and depletion of normal red blood cells causes the great fatigue of anemia.

Sickle cell disease was the first inherited illness linked to a molecular abnormality, but it wasn’t the first known condition that results from a mutation in the beta globin genes. In 1925, Thomas Cooley and Pearl Lee described severe anemia in Italian children, and in the decade following, others described a milder version of “Cooley’s anemia,” also in Italian children. The disease was named thalassemia, from the Greek for “sea,” in light of its high prevalence in the Mediterranean area. The two disorders turned out to be the same. The severe form, sometimes called thalassemia major, results from a homozygous mutation in the beta globin gene. The milder form, called thalassemia minor, affects some individuals who are heterozygous for the mutation.

Once researchers had worked out the structure of hemoglobin, and learned that different globins function in the embryo and fetus, the molecular basis of thalassemia became clear. The disorder that is common in the Mediterranean is more accurately called beta thalassemia (OMIM 141900), because the symptoms result from too few beta globin chains. Without them, not enough hemoglobin molecules are assembled to effectively deliver oxygen to tissues. Fatigue and bone pain arise during the first year of life as the child depletes fetal hemoglobin, and the “adult” beta globin genes are not transcribed and translated on schedule.

As severe beta thalassemia progresses, red blood cells die because the excess of alpha globin chains prevents formation of hemoglobin molecules. Liberated iron slowly destroys the heart, liver, and endocrine glands. Periodic blood transfusions can control the anemia, but they hasten iron buildup and organ damage. Drugs called chelators that entrap the iron can extend life past early adulthood, but they are very costly and not available in developing nations.



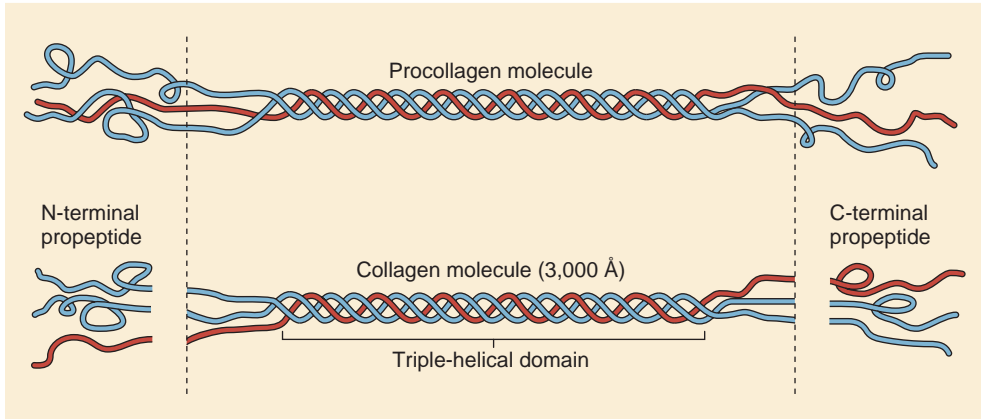
**Figure 12.2 Sickle cell disease results from a single DNA base change that substitutes one amino acid in the protein (valine replaces glutamic acid).** The result is a change in the surfaces of the molecules that causes aggregation into long, curved rods that deform the red blood cell.

Disorders of Orderly Collagen

Much of the human body consists of the protein collagen, a major component of connective tissue. Collagen accounts for more than 60 percent of the protein in bone and cartilage and provides 50 to 90 percent of the dry weight of skin, ligaments, tendons, and the dentin of teeth. Collagen is in parts of the eyes and the blood vessel linings, and it separates cell types in tissues.

Genetic control of collagen synthesis and distribution is complex; more than thirty-five collagen genes encode more than twenty types of collagen molecules. Other genes affect collagen, too. Mutations in the genes that encode collagen, not surprisingly, lead to a variety of medical problems (table 12.1). These disorders are particularly devastating, not only because collagen is nearly everywhere, but because collagen has an extremely precise conformation that is easily disrupted, even by slight alterations that might have little effect in proteins with other shapes (figure 12.3).

Collagen is sculpted from a longer precursor molecule called procollagen, which consists of many repeats of the amino acid sequence glycine-proline-modified proline. Three procollagen chains entwine. Two of the chains are identical and are encoded by one gene, and the other is encoded by a second gene. The electrical charges and



**Figure 12.3** Collagen has a very precise conformation. The  $\alpha 1$  collagen gene encodes the two blue polypeptide chains, and the  $\alpha 2$  procollagen gene encodes the third (red) chain. The procollagen triple helix is shortened before it becomes functional, forming the fibrils and networks that comprise much of the human body.

interactions of these amino acids with water coil the procollagen chains into a very regular triple helix, with space in the middle only for tiny glycine. The ragged ends of the polypeptides are snipped off by enzymes to form mature collagen. The collagen fibrils continue to associate with each other outside the cell, building the fibrils and networks that hold the body together. So important is the precision of collagen formation that a mutation that impairs the enzyme that places a single hydroxyl chemical group ( $\text{OH}^-$ ) on collagen causes a severe form of osteogenesis imperfecta (“brittle bone disease”), described in chapter 5 and shown in figure 3.22a.



**Figure 12.4** A disorder of connective tissue produces stretchy skin. A mutation that blocks trimming of procollagen chains to produce collagen causes the stretchy skin of Ehlers-Danlos syndrome type I.

**Table 12.1**  
Some Collagen Disorders

Disorder	OMIM	Genetic Defect (Genotype)	Signs and Symptoms (Phenotype)
Alport syndrome	203780	Mutation in type IV collagen interferes with tissue boundaries	Deafness and inflamed kidneys
Aortic aneurysm	100070	Missense mutation substitutes <i>arg</i> for <i>gly</i> in $\alpha 1$ gene	Aorta bursts
Chondrodysplasia	302950	Deletion, insertion, or missense mutation replaces <i>gly</i> with bulky amino acids	Stunted growth, deformed joints
Dystrophic epidermolysis bullosa	226600	Collagen fibrils that attach epidermis to dermis break down	Skin blisters on any touch
Ehlers-Danlos syndrome	130050	Missense mutations replace <i>gly</i> with bulky amino acids; deletions or missense mutations disrupt intron/exon splicing	Stretchy, easily scarred skin, lax joints
Osteoarthritis	165720	Missense mutation substitutes <i>cys</i> for <i>arg</i> in $\alpha 1$ gene	Painful joints
Osteogenesis imperfecta type I	166200	Inactivation of $\alpha$ allele reduces collagen triple helices by 50%	Easily broken bones; blue eye whites; deafness
Stickler syndrome	108300	Nonsense mutation in procollagen	Joint pain, degeneration of vitreous gel and retina



The boy in **figure 12.4** has a form of Ehlers-Danlos syndrome. A mutation prevents his procollagen chains from being cut, and collagen molecules cannot assemble. They form ribbonlike fibrils that lack the tensile strength to keep the skin from becoming too stretchy. Other collagen mutations cause missing procollagen chains, kinks in the triple helix, and defects in aggregation outside the cell.

Aortic aneurysm is a serious connective tissue disorder. It is part of the connective tissue disorder Marfan syndrome, the subject of the opening essay for chapter 10. Detection of mutations in either of the genes that cause the syndrome before symptoms arise can be lifesaving. An early sign is a weakened aorta. A person who knows that he or she has inherited a mutation can have frequent ultrasound exams to detect aortic weakening early enough to treat it surgically before it bursts.

## Early-Onset Alzheimer Disease

The story of the discovery of a mutation that causes an early-onset, autosomal dominant form of Alzheimer disease began in the 1880s, when a woman named Hannah, born in Latvia, developed progressive dementia. Hannah's condition was highly unusual; she was only in her early forties when the classic forgetfulness that heralds the disease's onset began. Apparently this form of the illness originated, in this family, in Hannah. Many of her descendants also experienced dementia, some as early as in their thirties. (Alois Alzheimer first described the disease that would bear his name in 1906, after studying a 51-year-old woman named Auguste D. He identified the accumulation of two types of protein in affected brains—plaques of amyloid beta and tangles of tau protein.)

In 1974, Hannah's grandson and great-grandson, both physicians, constructed an extensive pedigree tracing Alzheimer disease in their family. They circulated the pedigree among geneticists, hoping to elicit interest in identifying the family's mutation, offering their own and relatives' DNA for testing. Research teams in Mexico, the United States, and Canada began the search in 1983. By 1992, they narrowed the investigation to a portion of chromosome 14, and

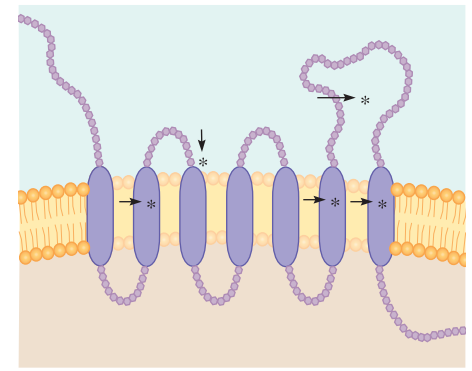
three years later, they pinpointed the gene. It encodes a protein called presenilin 1 (OMIM 104311) that acts as a receptor anchored in the membrane of a Golgi apparatus or a vesicle (**figure 12.5**). Normally, the protein monitors the cell's storage or use of amyloid beta, one of two proteins that accumulate in the brains of people with Alzheimer disease. Members of families that have early-onset Alzheimer disease due to a mutation in this gene have elevated levels of presenilin 1 in their bloodstreams before symptoms begin. Somehow the abnormality in presenilin disrupts amyloid production, folding, function, or degradation.

More than 160 mutations are known that substitute one amino acid for another in presenilin 1, impairing its function sufficiently to cause the amyloid beta buildup that eventually is associated with symptoms of Alzheimer disease. Mutations in at least four other genes can cause or increase the risk of developing Alzheimer disease. **Table 12.2** describes how a few other mutations impair health.

## One Disorder or Several?

Geneticists can be maddeningly inconsistent when assigning disease names to mutations. For one gene, different mutations may cause differing degrees of the same syndrome or different subsets of symptoms of that syndrome. Yet for another gene, different mutations cause different disorders. For example, all mutations in the *CFTR* gene cause cystic fibrosis—whether that includes the full spectrum of impaired breathing and digestion, or just male infertility. CF can affect different tissues in different individuals. Yet different mutations affecting the beta globin gene cause the clinically distinct sickle cell disease as well as beta thalassemia, although they both affect the same tissue, blood. Similarly, the little girl described in the chapter opening essay had two mutations in her beta globin genes, and two diseases—sickle cell disease and hemolytic anemia.

Adding to the inconsistency is a gene such as *lamin A* (OMIM 150330). Unlike *CFTR*, in which mutations cause variations of one disease, and beta globin, in which mutations cause different diseases of the same tissue, mutations in *lamin A* cause different disorders that affect very different



**Figure 12.5 One genetic cause of Alzheimer disease.** When geneticists searched the DNA of people with very early-onset inherited Alzheimer disease, they identified a gene on chromosome 14 whose protein product, shown here, is a receptor anchored into a membrane at seven points. This protein resides in vesicles derived from the Golgi apparatus. When abnormal, it cuts amyloid precursor proteins into abnormal-sized pieces that fuse and accumulate outside cells. Asterisks indicate sites where mutations in the gene disrupt the protein.

tissues. *Lamin A* mutations cause the rapid-aging disorder Hutchinson-Gilford progeria syndrome (see figure 3.22 and table 3.4), and at least six other conditions, including muscular dystrophies and a heart condition. *Lamin A* proteins form a network beneath the inner nuclear membrane that interacts with other proteins. Apparently different mutations affect *lamin A*'s interactions with other proteins that cause the diverse associated disorders.

*CFTR*, *beta globin*, and *lamin A* are single genes. Another source of confusion in assigning mutations to specific medical conditions is genetic heterogeneity—the same symptoms caused by mutations in different genes. Genetic heterogeneity is often due to mutations in genes whose products are part of the same biochemical pathway, as we saw in chapter 5 for the porphyrias. Until the pathway is identified, genetic heterogeneity appears as individuals with the symptoms of a known genetic disease who do not have the commonly recognized mutation. With the sequencing of the human genome, different ways to inherit known syndromes are being increasingly recognized.

Table 12.2

## How Mutations Cause Disease

Disorder	OMIM	Protein	Genetic Defect (Genotype)	Signs and Symptoms (Phenotype)
Cystic fibrosis	602421	Cystic fibrosis transmembrane regulator (CFTR)	Missing amino acid or other defect alters conformation of chloride channels in certain epithelial cell plasma membranes. Water enters cells, drying out secretions.	Frequent lung infection, pancreatic insufficiency
Duchenne muscular dystrophy	310200	Dystrophin	Deletion eliminates dystrophin, which normally binds to inner face of muscle cell plasma membranes, maintaining cellular integrity. Cells and muscles weaken.	Gradual loss of muscle function
Familial hypercholesterolemia	143890	LDL receptor	Deficient LDL receptors cause cholesterol to accumulate in blood.	High blood cholesterol, early heart disease
Hemophilia A	306700	Factor VIII	Absent or deficient clotting factor causes hard-to-control bleeding.	Slow or absent blood clotting
Huntington disease	143100	Huntingtin	Extra bases in the gene add amino acids to the protein product, which impairs certain transcription factors and proteasomes.	Uncontrollable movements, personality changes
Marfan syndrome	154700	Fibrillin or transforming growth factor $\beta$ receptor	Deficient connective tissue protein in lens and aorta.	Long limbs, weakened aorta, spindly fingers, sunken chest, lens dislocation
Neurofibromatosis type 1	162200	Neurofibromin	Defect in protein that normally suppresses activity of a gene that causes cell division.	Benign tumors of nervous tissue beneath skin

## Key Concepts

1. Mutations add, delete, or rearrange genetic material in a germline cell or somatic cell.
2. In sickle cell disease, a mutation causes hemoglobin to crystallize in a low-oxygen environment, bending red blood cells into sickle shapes and impairing circulation. In beta thalassemia, beta globin is absent or scarce, depleting hemoglobin molecules.
3. Mutations in collagen genes can disrupt the protein's precise organization.
4. In one form of Alzheimer disease, a mutation in a receptor protein leads to amyloid beta buildup.
5. Mutations in a gene may cause either different versions of the same disease or distinct illnesses.

## 12.2 Causes of Mutation

A mutation can occur spontaneously or be induced by exposure to a chemical or radiation. An agent that causes mutation is called a **mutagen**.

### Spontaneous Mutation

A spontaneous mutation can be a surprise. For example, two healthy people of normal height may have a child with achondroplasia, an autosomal dominant form of dwarfism. How could this happen when no other family members are affected? If the mutation is dominant, why are the parents of normal height? The child has a genetic condition, but he did not inherit it. Instead, he originated it. His siblings have no higher risk of inheriting the condition than anyone in the general population, but each of his children will face a 50 percent chance of inheriting it. The boy's achondroplasia arose from a *de novo*, or new, mutation in a parent's gamete. This is a spontaneous mutation—that is, it is not caused by a mutagen. A spontaneous mutation usually originates as an error in DNA replication.

One cause of spontaneous mutation stems from the chemical tendency of free nitrogenous bases to exist in two slightly different structures, called tautomers. For extremely short times, each base is in an unstable tautomeric form. If, by chance, such an unstable base is inserted into newly forming DNA, an error will be generated and perpetuated when that strand replicates.

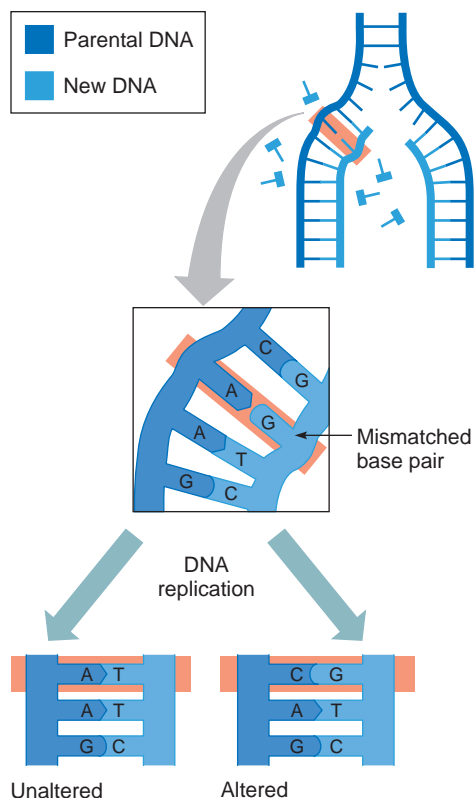
**Figure 12.6** shows how this can happen.

### Spontaneous Mutation Rate

The spontaneous mutation rate varies for different genes. The gene that, when mutant, causes neurofibromatosis type 1 (NF1), for example, has a very high mutation rate, arising in 40 to 100 of every million gametes (**table 12.3**). NF1 affects 1 in 3,000 births, about half in families with no prior cases. The gene's large size may contribute to its high mutability—there are more ways for its sequence to change, just as there are more opportunities for a misspelling to occur in a long sentence than in a short one.

Based on the prevalence of certain disease-causing genes, geneticists estimate that each human gene has about a 1 in 100,000 chance of mutating. Each of us probably carries a few new spontaneously mutated genes. Mitochondrial genes mutate at a higher rate than nuclear genes because they cannot repair DNA (see section 12.6.)

Estimates of the spontaneous mutation rate for a particular gene are usually derived from observations of new, dominant conditions, such as achondroplasia in the boy. This is possible because a new dominant mutation is detectable simply by observing the phenotype. In contrast, a new recessive mutation would not be obvious until two heterozygotes



**Figure 12.6 Spontaneous mutation.** DNA bases are very slightly chemically unstable, and fleetingly they exist in alternate forms. If a replication fork encounters a base in its unstable form, a mismatched base pair can result. After another round of replication, one of the daughter cells has a different base pair than the one in the corresponding position in the original DNA. (This figure depicts two rounds of DNA replication.)

produced a homozygous recessive offspring with a noticeable phenotype.

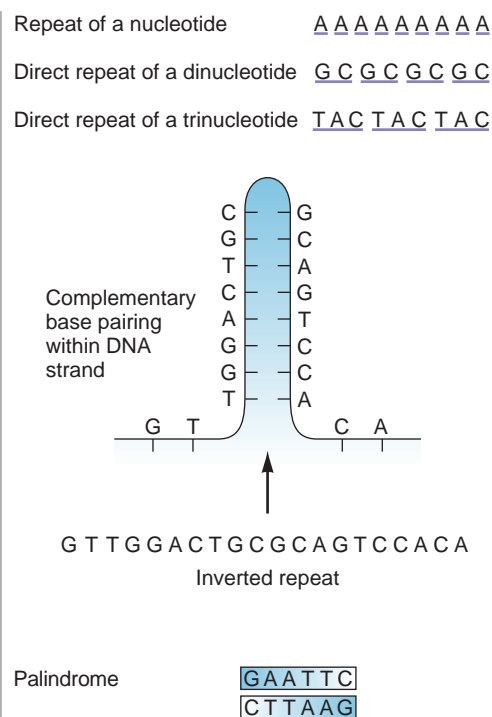
The spontaneous mutation rate for autosomal genes can be estimated using the formula: number of *de novo* cases/ $2X$ , where  $X$  is the number of individuals examined. The denominator has a factor of 2 to account for the nonmutated homologous chromosome.

Spontaneous mutation rates in human genes are difficult to assess because our generation time is long—usually 20 to 30 years. In bacteria, a new generation arises every half hour or so, and mutation is therefore much more frequent. The genetic material of viruses also spontaneously mutates rapidly.

### Mutational Hot Spots

In some genes mutations are more likely to occur in regions called hot spots, where sequences are repetitive. It is as if the molecules that guide and carry out replication become “confused” by short repeated sequences, much as an editor scanning a manuscript might miss the spelling errors in the words “happyness” and “bananana” (figure 12.7). For example, more than one-third of the many mutations that cause alkaptonuria occur at or near one or more CCC repeats, even though these repeats account for only 9 percent of the gene (see the opening essay for chapter 5).

The increased incidence of mutations in repeats has a physical basis. Within a gene, when DNA strands locally unwind to replicate in symmetrical or repeated sequences,



**Figure 12.7 DNA symmetry may increase the likelihood of mutation.** These examples show repetitive and symmetrical DNA sequences that may “confuse” replication enzymes, causing errors.

bases located on the same strand may pair. (This is similar to RNA strands forming hairpin loops.) For example, a stretch of ATATAT pairs with TATATA elsewhere on the same strand. This pairing interferes with replication and repair enzymes, increasing the chance of an error. For example,

**Table 12.3**

**Mutation Rates of Some Genes That Cause Inherited Disease**

Disorder	OMIM	Mutations per Million Gametes	Signs and Symptoms (Phenotype)
X-linked			
Duchenne muscular dystrophy	310200	40–105	Muscle atrophy
Hemophilia A	306700	30–60	Severe impairment of blood clotting
Hemophilia B	306900	0.5–10	Mild impairment of blood clotting
Autosomal Dominant			
Achondroplasia	100800	10	Very short stature
Aniridia	106200	2.6	Absence of iris
Huntington disease	143100	<1	Uncontrollable movements, personality changes
Marfan syndrome	154700	4–6	Long limbs, weakened blood vessel walls
Neurofibromatosis type 1	162200	40–100	Brown skin spots, benign tumors under skin
Osteogenesis imperfecta	166200	10	Easily broken bones
Polycystic kidney disease	600666	60–120	Benign growths in kidneys
Retinoblastoma	180200	5–12	Malignant tumor of retina



mutations in the gene for clotting factor IX, which causes hemophilia B, occur 10 to 100 times as often at any of 11 sites in the gene that have extensive direct repeats of CG.

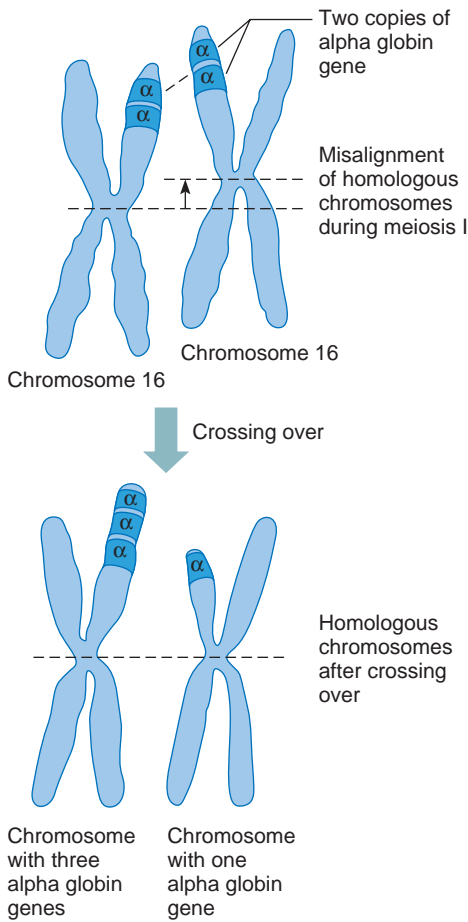
Small additions and deletions of DNA bases are more likely to occur near sequences called palindromes (see figure 12.7). These sequences read the same, in a 5' to 3' direction, on complementary strands. Put another way, the sequence on one strand is the reverse of the sequence on the complementary strand. Palindromes probably increase the spontaneous mutation rate by disturbing replication.

The blood disorder alpha thalassemia (OMIM 141800) illustrates the confusing effect of direct (as opposed to inverted) repeats of an entire gene. A person who does not have the disorder has four genes that specify alpha globin chains, two next to each other on each chromosome 16. Homologs with repeated genes can misalign during meiosis when the first sequence on one chromosome lies opposite the second sequence on the homolog. Crossing over can result in a sperm or oocyte that has one or three alpha globin genes instead of the normal two (figure 12.8). Fertilization with a normal gamete then results in a zygote with one extra or one missing alpha globin gene. At least three dozen diseases result from this unequal crossing over.

The number of alpha globin genes affects health, because the number of proteins reflects the numbers of genes being actively transcribed. A person with only three alpha globin genes produces enough hemoglobin, and is a healthy carrier. Individuals with only two copies of the gene are mildly anemic and tire easily, and a person with a single alpha globin gene is severely anemic. A fetus lacking alpha globin genes does not survive.

### Induced Mutation

Researchers can sometimes infer a gene's normal function by observing what happens when mutation alters it. Because the spontaneous mutation rate is far too low to be a practical source of genetic variants for experiments, researchers make mutants. Geneticists use mutagens on model organisms to infer normal gene functions, yielding many collections and insights into human health.



**Figure 12.8 Gene duplication and deletion.** The repeated alpha globin genes are prone to mutation by mispairing during meiosis.

### Intentional Use of Mutagens

Chemicals or radiation are used to induce mutation. Alkylating agents, for example, are chemicals that remove a DNA base, which is

replaced with any of the four bases—three of which are a mismatch against the complementary strand. Dyes called acridines add or remove a single DNA base. Because the DNA sequence is read three bases in a row, adding or deleting a single base can destroy a gene's information, altering the amino acid sequence of the encoded protein. Several other mutagenic chemicals alter base pairs, so that an A-T replaces a G-C, or vice versa. X rays and other forms of radiation delete a few bases or break chromosomes.

Researchers have developed several ways to test the mutagenicity of a substance. The best known, the Ames test, assesses how likely a substance is to harm the DNA of rapidly reproducing bacteria. One version of the test uses a strain of *Salmonella* that cannot grow when the amino acid histidine is absent from its medium. If exposure to a substance enables bacteria to grow on the deficient medium, then a gene has mutated that allows it to do so. Another variation of the Ames test uses mammalian liver tissue to make the results more like those of an animal. Because many mutagens are also carcinogens (cancer-causing agents), the substances that the Ames test identifies as mutagens may also cause cancer. **Table 12.4** lists some common mutagens.

In another variation of the Ames test, researchers exposed human fibroblasts (connective tissue cells) growing in culture to liquefied cigarette smoke. The chemicals from the smoke cut chromosomes through both DNA strands. This is an especially damaging insult because broken chromosomes can join with each other in different ways that can activate cancer-causing genes. Hence,

**Table 12.4**  
Commonly Encountered Mutagens

Mutagen	Source
Aflatoxin B	Fungi growing on peanuts and other foods
2-amino 5-nitrophenol	Hair dye components
2,4-diaminoanisole	"
2,5-diaminoanisole	"
2,4-diaminotoluene	"
p-phenylenediamine	"
Furylfuramide	Food additive
Nitrosamines	Pesticides, herbicides, cigarette smoke
Proflavine	Antiseptic in veterinary medicine
Sodium nitrite	Smoked meats
Tris (2,3-dibromopropyl phosphate)	Flame retardant in children's sleepwear

the experiment may have modeled one way that cigarettes cause cancer.

A limitation of using a mutagen is that it cannot cause a specific mutation. In contrast, a technique called site-directed mutagenesis changes a gene in a desired way. A gene is mass-produced, but it includes an intentionally substituted base, just as an error in a manuscript is printed in every copy of a book. Site-directed mutagenesis is faster and more precise than waiting for nature or a mutagen to produce a useful variant. It also makes it possible to study lethal mutations that can theoretically exist, but never do because they are so drastic that development does not proceed very far. Researchers can study such a lethal mutation in cell culture, or in model organisms before they cease developing.

Accidental Exposures to Mutagens

Some mutagen exposure is unintentional. This occurs from workplace contact before the danger is known; from industrial accidents; from medical treatments such as chemotherapy and radiation; and from exposure to weapons that emit radiation.

An environmental disaster that released mutagenic radiation was a steam explosion at a nuclear reactor in the former Soviet Union on April 25, 1986. Between 1:23 and 1:24 A.M., Reactor 4 at the Chernobyl Nuclear Power Station in Ukraine exploded, sending a great plume of radioactive isotopes into the air that spread for thousands of miles. The reactor had been undergoing a test, its safety systems temporarily disabled, when it overloaded and rapidly flared out of control. Twenty-eight people died of acute radiation exposure in the days following the explosion.

Acute radiation poisoning is not genetic. Evidence of a mutagenic effect is the increased rate of thyroid cancer among children who were living in nearby Belarus. Rates have multiplied tenfold. The thyroid glands of young people soak up iodine, which in a radioactive form bathed Belarus in the days after the explosion. Cancer rates have also risen among workers who cleaned up the disaster. Analysis of radiation exposure in their teeth is being used to assess whether cancer risk rises with degree of exposure.

Another way researchers tracked mutation rates after the Chernobyl explosion

Table 12.5 Sources of Radiation Exposure

Source	Percentage of Total
Natural (cosmic rays, sunlight, earth's crust)	81%
Medical X rays	11%
Nuclear medicine procedures	4%
Consumer products	3%
Other (nuclear fallout, occupational)	<1%

was to compare the lengths of short DNA repeats called minisatellite sequences in children born in 1994 and in their parents, who lived in the Mogilev district of Belarus at the time of the accident and have remained there. Minisatellites are the same length within all cells of an individual. A minisatellite size in a child that does not match the size of either parent indicates that a mutation occurred in a parent's gamete. Such a mutation was twice as likely to occur in exposed families as in control families living elsewhere. Mutation rates of nonrepeated DNA sequences are too low to provide useful information on the effects of radiation exposure, so investigators track minisatellites as a sensitive test of change.

Researchers learned of a new type of mutation from a young man conceived within a week of the Chernobyl accident, near the disaster site. He has extra digits, an abnormal epiglottis, and a benign growth on the hypothalamus, a group of symptoms called Pallister-Hall syndrome (OMIM 146510). On his way to a camp for "children of Chernobyl" in the summer of 2002, he stopped at the National Institutes of Health to provide a DNA sample. Researchers indeed found a mutation in the gene on chromosome 7 known to cause the syndrome—a 72-base insertion that causes a "stop" codon to form, shortening the encoded protein. Oddly, the insertion matched mitochondrial DNA sequences. Apparently, the radiation damaged mitochondria in the sperm or oocyte, sending some mitochondrial DNA into the nucleus, where it inserted into the Pallister-Hall gene. Another clue to the unusual origin of this young man's condition is that it is autosomal dominant, but neither of his parents have it. Since his case, researchers have discovered 27 such "nuclear DNA sequences of mitochondrial origin."

Natural Exposure to Mutagens

Simply being alive exposes us to radiation that can cause mutation. Natural environmental sources of radiation include cosmic rays, sunlight, and radioactive minerals in the earth's crust, such as radon. Contributions from medical X rays and occupational radiation hazards are comparatively minor (table 12.5). Job sites with increased radiation exposure include weapons facilities, research laboratories, health care facilities, nuclear power plants, and certain manufacturing plants. Radiation exposure is measured in units called millirems; the average annual exposure in the northern hemisphere is 360 millirems.

Most of the potentially mutagenic radiation we are exposed to is of the ionizing type, which means that it has sufficient energy to remove electrons from atoms. Unstable atoms that emit ionizing radiation both exist naturally and are made by humans. Ionizing radiation breaks the DNA sugar-phosphate backbone.

Ionizing radiation is of three major types. Alpha radiation is the least energetic and most short-lived, and the skin absorbs most of it. Uranium and radium emit alpha radiation. Beta radiation can penetrate the body farther, and emitters include tritium (a form of hydrogen), carbon-14, and strontium-90. Both alpha and beta rays tend not to harm health, although they can do damage if inhaled or eaten. In contrast is the third type of ionizing radiation, gamma rays. These can penetrate the body, damaging tissues. Plutonium and cesium isotopes used in weapons emit gamma rays, and this form of radiation is used to kill cancer cells.

X rays are the major source of exposure to human-made radiation, and they are not

a form of ionizing radiation. They have less energy and do not penetrate the body to the extent that gamma rays do.

The effects of radiation damage to DNA depend upon the functions of the mutated genes. Mutations in oncogenes or tumor suppressor genes, discussed in chapter 18, can cause cancer. Radiation damage can be widespread, too. Exposing cells to radiation and then culturing them causes a genome-wide destabilization, so that mutations may occur even after the cell has divided a few times. Cell culture studies have also identified a “bystander effect,” when radiation seems to harm cells not directly exposed.

Chemical mutagens are in the environment, too. Evaluating the risk that a specific chemical exposure will cause a mutation is very difficult, largely because people vary greatly in inherited susceptibilities, and are exposed to many chemicals. The risk that exposure to a certain chemical will cause a mutation is often less than the natural variability in susceptibility within a population, making it nearly impossible to track the true source and mechanism of any mutational event. Human genome sequence information can be used to determine specific inherited risks for specific employees who might encounter a mutagen in the workplace. However, such testing raises ethical concerns.

### Key Concepts

- 1. Genes have different mutation rates.
- 2. Spontaneous mutations result when rare base tautomers are incorporated during replication.
- 3. Spontaneous mutations are more frequent in microorganisms and viruses because they reproduce often and lack DNA repair.
- 4. Mutations are more likely to happen when the nearby DNA is repetitive or symmetrical.
- 5. Mutagens are chemicals or radiation that increase the risk of mutation. Researchers use mutagens to more quickly obtain mutants, which reveal normal gene function. Site-directed mutagenesis creates and amplifies specific mutations.
- 6. Mutagen exposure can be accidental.
- 7. Some radiation sources are natural.

## 12.3 Types of Mutations

Mutations can be classified by whether they remove, alter, or add a function. Mutations are also classified by exactly how they structurally alter DNA. **Table 12.6** summarizes the types of mutations described in this section using an analogy to an English sentence.

### Point Mutations

A **point mutation** is a change in a single DNA base. It is a **transition** if a purine replaces a purine (A to G or G to A) or a pyrimidine replaces a pyrimidine (C to T or T to C). It is a **transversion** if a purine replaces a pyrimidine or vice versa (A or G to T or C). A point mutation can have any of several consequences—or it may have no obvious effect at all on the phenotype, acting as a silent mutation.

### Missense and Nonsense Mutations

A point mutation that changes a codon that normally specifies a particular amino acid into one that codes for a different amino acid is called a **missense mutation**. If the substituted amino acid alters the protein’s conformation significantly or occurs at a

site critical to its function, signs or symptoms of disease or an observable variant of a trait may result.

The point mutation that causes sickle cell disease (see figure 12.2) is a missense mutation. The DNA sequence CTC encodes the mRNA codon GAG, which specifies glutamic acid. In sickle cell disease, the mutation changes the DNA sequence to CAC, which encodes GUG in the mRNA, which specifies valine. This mutation changes the protein’s shape, which alters its function.

A point mutation that changes a codon specifying an amino acid into a “stop” codon—UAA, UAG, or UGA in mRNA—is a **nonsense mutation**. A premature stop codon shortens the protein product, which can profoundly influence the phenotype. Nonsense mutations are predictable by considering which codons can mutate to a “stop” codon.

An example of a nonsense mutation is one responsible for the most common cause of factor XI deficiency (OMIM 264900), a blood clotting disorder. A GAA codon specifying glutamic acid is changed to UAA, signifying “stop.” The shortened clotting factor cannot halt the profuse bleeding that occurs during surgery or from injury. In the opposite situation, when a normal stop codon mutates into a codon that specifies an

Table 12.6  
Types of Mutations

A sentence comprised of three-letter words can provide an analogy to the effect of mutations on a gene’s DNA sequence:	
Normal	THE ONE BIG FLY HAD ONE RED EYE
Missense	THQ ONE BIG FLY HAD ONE RED EYE
Nonsense	THE ONE BIG [ ]
Frameshift	THE ONE QBI GFL YHA DON ERE DEY
Deletion	THE ONE BIG [ ] HAD ONE RED EYE
Insertion	THE ONE BIG WET FLY HAD ONE RED EYE
Duplication	THE ONE BIG FLY FLY HAD ONE RED EYE
Expanding mutation	
generation 1	THE ONE BIG FLY HAD ONE RED EYE
generation 2	THE ONE BIG FLY FLY FLY HAD ONE RED EYE
generation 3	THE ONE BIG FLY FLY FLY FLY FLY HAD ONE RED EYE



amino acid, the resulting protein is longer than normal, because translation continues through what is normally a stop codon.

Point mutations may exert profound effects by controlling how transcription proceeds. For example, in 15 percent of people who have Becker muscular dystrophy (OMIM 310200)—a milder adult form of the condition—the muscle protein dystrophin is normal, but its levels are reduced. The mutation causing the protein shortage is in the promoter for the dystrophin gene. This slows transcription, and dystrophin protein is scarce. Muscle function suffers. In contrast, the other 85 percent of individuals who have Becker muscular dystrophy have shortened proteins, not a deficiency of normal-length proteins.

Another way that point mutations can affect protein production is to disrupt the trimming of long precursor molecules. Such a mutation causes the type of Ehlers-Danlos syndrome that affects the boy in figure 12.4.

## Splice Site Mutations

A point mutation can greatly affect a gene's product if it alters a site where introns are normally removed from the mRNA. This is called a splice site mutation. It can affect the phenotype if an intron is translated into amino acids, or if an exon is skipped instead of being translated, shortening the protein.

Retaining an intron is unusual because most introns have stop codons in all reading frames. However, if a stop codon is not encountered, a retained intron adds bases to the protein-coding portion of an mRNA. For example, in one family with severe cystic fibrosis, a missense mutation alters an intron site so that it is not removed. The encoded protein is too bulky to move to its normal position in the plasma membrane.

A missense mutation need not alter the amino acid sequence to cause harm if it disrupts intron/exon splicing. For example, a missense mutation in the *BRCA1* breast cancer gene went undetected for a long time because it does not alter the amino acid sequence. Instead, the protein is missing several amino acids. The missense mutation creates an intron splicing site where there should not be one, and an entire exon

is “skipped” when the mRNA is translated into protein, as if it were an intron. This mutation, therefore, is a deletion at the mRNA level. At the DNA level, it is a missense mutation.

A disorder called familial dysautonomia (OMIM 223900)(FD) usually results from a splice site mutation that causes skipping of an exon in the gene encoding an enzyme (I-kappa beta-kinase-associated protein). Symptoms reflect the loss of certain neurons that control sensation and involuntary responses. The *In Their Own Words* box in this chapter describes life for a child with FD.

A peculiarity of some disorders caused by exon-skipping mutations is that some cells seem to ignore the problem, manufacturing a normal protein from the affected gene—after all, the amino acid sequence information is still there. Depending upon which cells actually make the encoded protein, the phenotype may be less severe than in individuals with the same disorder but with a different type of mutation in an exon.

Studies on various cell types from individuals with FD or who have died from the disease reveal that the cells in which the exon is skipped are the cells that contribute to symptoms. That is, many cells from the brain and spinal cord skip the exon, but cells from muscle, lung, liver, white blood cells, and various glands produce normal-length proteins. This means there may be a way to coax nervous system cells in affected children to also produce the protein. Current clinical trials are examining the ability of several natural compounds to restore normal processing of the FD gene's information.

## Deletions and Insertions Can Shift the Reading Frame

In genes, the number three is very important, because triplets of DNA bases specify amino acids. Adding or deleting a number of bases that is not a multiple of three devastates a gene's function because it disrupts the gene's reading frame, which refers to the nucleotide position where the DNA begins to encode protein. An exon is usually “readable” (has no stop codons) in only one of its three possible reading frames. A change that

alters the reading frame is called a **frameshift mutation**. Line 4 in table 12.6 illustrates a frameshift mutation.

A **deletion mutation** removes genetic material. A deletion that removes three or a multiple of three bases will not cause a frameshift, but can still alter the phenotype. Deletions range from a single DNA nucleotide to thousands of bases to larger pieces of chromosomes. Chapter 13 considers large deletions. Many common inherited disorders result from deletions. About two-thirds of people with Duchenne muscular dystrophy, for example, are missing large sections of the huge gene that encodes dystrophin. Many cases of male infertility are caused by tiny deletions in the Y chromosome.

An **insertion mutation** adds DNA and it, too, can offset a gene's reading frame. In one form of Gaucher disease, for example, an inserted single DNA base prevents production of an enzyme that normally breaks down glycolipids in lysosomes. The resulting buildup of glycolipid enlarges the liver and spleen and causes easily fractured bones and neurological impairment. Gaucher disease is common among Jewish people of eastern European descent. Although most cases arise from a missense mutation, some families have the insertion mutation. Gaucher disease illustrates how different types of mutations in the same gene cause the same or a similar phenotype.

Another type of insertion mutation repeats part of a gene's sequence. The insertion is usually adjacent or close to the original sequence, like a typographical error repeating a word word. Two copies of a gene next to each other is called a **tandem duplication**. A form of Charcot-Marie-Tooth disease (OMIM 118200), which causes numb hands and feet, results from a one-and-a-half-million-base-long tandem duplication.

**Figure 12.9** compares the effects on protein sequence of missense, nonsense, and frameshift mutations in the gene that encodes the LDL receptor, causing familial hypercholesterolemia (see figure 5.2). These three mutations exert very different effects on the protein. A missense mutation replaces one amino acid with another, bending the protein in a way that impairs its function. A nonsense mutation is much more drastic, shortening the protein. A frameshift mutation introduces



### Familial Dysautonomia: Rebekah's Story

Our daughter Rebekah has familial dysautonomia. This is a rare genetic disorder that affects the autonomic and peripheral nervous systems. Rebekah was born in 1992, but she was not diagnosed until she was almost three. She appeared to be healthy at birth, but she began to decline rapidly by nine months. Rebekah suffered from frequent pneumonia, vomiting and retching, extremely high fevers, chills, rapid heartbeat, and seizures. At times, she would become covered with hot, red blotches. Other times, her hands and feet got very cold and appeared puffy and blue. Episodes of crying would precipitate breathholding, when she would turn blue and lose consciousness. As she lost ground on the growth and development charts, medical testing failed to reveal a cause for these symptoms. We wondered if we would identify the problem before she died. Our physicians sometimes hinted that perhaps we were the cause.

After more than twelve local hospitalizations and a variety of tests, we traveled to a major children's teaching hospital, hoping that a fresh team of doctors would identify Rebekah's condition. One doctor knew immediately that she had FD. He recognized the pattern of "dysautonomic crises." Two more symptoms, which we hadn't even noticed, were diagnostic indicators. Individuals with FD do not cry tears, and they lack papillae (bumps) on the tip of the tongue. Our Eastern European, Jewish heritage was also a clue, because FD is one of a number of diseases primarily affecting this population.

To a varying degree, FD reduces sensation of pain, heat, and cold. There are problems with balance and coordination, including motor difficulties that affect feeding, swallowing, and breathing. Most people with FD have a feeding tube, and must limit what they eat or drink by mouth due to danger of aspiration. FD causes fluctuations in blood pressure, digestive problems, and learning disabilities. Most individuals develop scoliosis, usually requiring corrective spine surgery. In short, FD affects every organ and system in the body.

The diagnosis allowed us to finetune Rebekah's therapies and activities to maximize her well-being. With improved nutrition, excellent therapies, and wonderful teachers, Rebekah has made tremendous progress, but we are always poised for a hospital stay. Even a minor illness can set off a crisis. A team of pediatric specialists monitors her lungs, heart, eyes, back, and growth and development.

Rebekah is a happy, good-natured child who makes friends easily and is sensitive to the needs of others. She works hard in school, and is able to keep up when her health is good. She has learned to overcome her learning challenges, using assistive technology in school to help her with writing and organizing. When Rebekah got a back brace to try to slow the scoliosis, and I tried to steer her to choose clothes that would deemphasize the bulk of the brace, she told me, "Mom, just relax. They're going to see it sooner or later!"



**Figure 1** Rebekah with her dog, Tracy.

We don't know what the future holds. FD is a progressive, degenerative disease with life-threatening complications and a shortened lifespan. Any major stress, including developmental changes, surgery, a serious illness, and increased emotional stress, can exacerbate the severity. Yet, we feel hopeful for our daughter's future. We are most encouraged by Rebekah herself. Her positive outlook on life, her willingness to find the good in any situation, and her ability to overcome challenges with spunk and humor inspire everyone around her.

Lynn Lieberman

a section of amino acids not normally part of the protein.

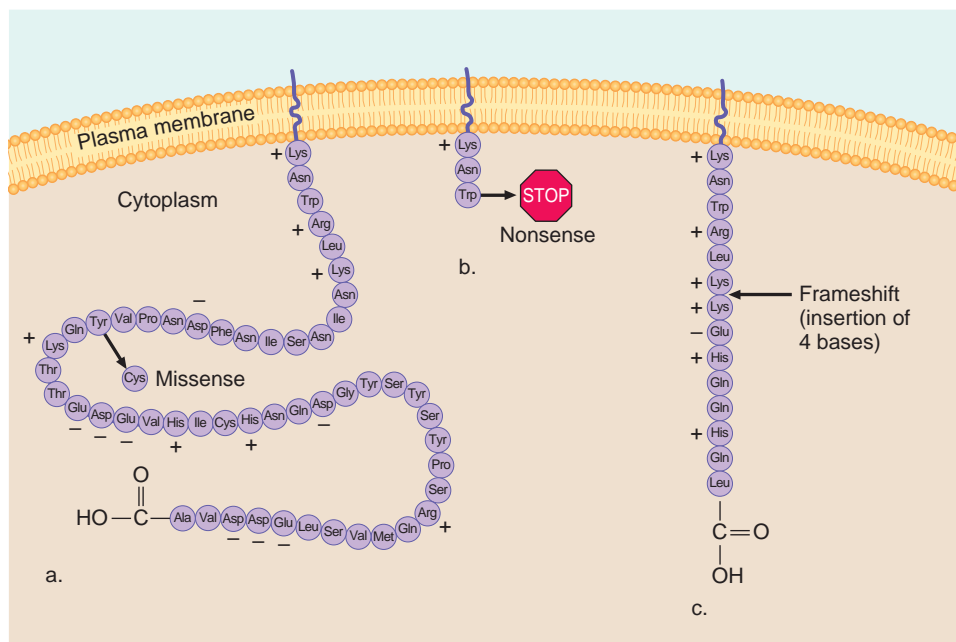
### Pseudogenes and Transposons Revisited

Recall from chapter 11 that a pseudogene is a DNA sequence that is very similar to that

of a protein-encoding gene. A pseudogene is not translated into protein, although it may be transcribed. The pseudogene may have descended from the original gene sequence, which was duplicated when DNA strands misaligned during meiosis, similar to the situation depicted in figure 12.8 for the alpha globin gene. When this happens, a gene and

its copy end up right next to each other on the chromosome. The original gene or the copy then mutates to such an extent that it is no longer functional and becomes a pseudogene. Its duplicate lives on as the functional gene.

Although a pseudogene is not translated, its presence can interfere with the expression of the functional gene and cause



**Figure 12.9** Different mutations in a gene can cause the same disorder. In familial hypercholesterolemia, several types of mutations alter the LDL receptor normally anchored in the plasma membrane. LDL receptor **(a)** bears a missense mutation—a cysteine substitutes for a tyrosine bending the receptor enough to impair its function. The short LDL receptor in **(b)** results from a nonsense mutation, in which a stop codon replaces a tryptophan codon. In **(c)**, a 4-base insertion alters the reading frame.

a mutation. For example, some cases of Gaucher disease result from a crossover between the working gene and its pseudogene, which has 96 percent of the same sequence 16,000 bases away. The result is a fusion gene, which is a sequence containing part of the functional gene and part of the pseudogene. The fusion gene does not retain enough of the normal gene sequence to enable the cell to synthesize the encoded enzyme. Gaucher disease results. As previously mentioned, this is a lysosomal storage disease whose symptoms include fatigue, bruising, anemia, and weak bones. For many patients, supplying the enzyme eliminates symptoms.

Chapter 11 also considered transposons, or “jumping genes.” Transposons can alter gene function in several ways. They can disrupt the site they jump from, shut off transcription of the gene they jump into, or alter the reading frame of their destination if they are not a multiple of three bases. For example, a boy with X-linked hemophilia A had a transposon in his factor VIII gene—a sequence that was also in his carrier mother’s genome, but on her chromosome 22. Apparently, in the oocyte, the transposon

jumped into the factor VIII gene on the X chromosome, causing the boy’s hemophilia.

## Expanding Repeats

Until 1992, myotonic dystrophy was very puzzling because it worsened and began at

an earlier age as it passed from one generation to the next. This phenomenon is called “anticipation,” and for many years it was thought to be psychological. A grandfather might experience only mild weakness in his forearms, and cataracts. His daughter might have more noticeable arm and leg weakness, and a flat facial expression. Her affected children might experience severe muscle weakness.

With the ability to sequence genes, researchers found that myotonic dystrophy indeed worsens with each generation because the gene expands! Myotonic dystrophy is caused by a type of mutation called an expanding triplet repeat. The gene, on chromosome 19, has an area rich in repeats of the DNA triplet CTG. A person who does not have myotonic dystrophy usually has from 5 to 37 copies of the repeat, whereas a person with the disorder has from 50 to thousands of copies (**figure 12.10**).

Expanding triplet repeats have been discovered in more than fifteen human inherited disorders. Usually, a repeat number of fewer than 40 copies is stably transmitted to the next generation and doesn’t produce symptoms. Larger repeats are unstable, enlarging with each generation and causing symptoms that are more severe and begin sooner. Reading 12.1 describes the triplet repeat disorder fragile X syndrome.

Myotonic Dystrophy			
Pedigree	Age of onset	Phenotype	Number of copies of GAC mRNA repeat
I 1 (unaffected female) × 2 (affected male)	Older adulthood	Mild forearm weakness, cataracts	50–80
II 1 (affected female) × 2 (unaffected male)	Mid-adulthood	Moderate limb weakness	80–700
III 1 (affected male), 2 (unaffected female), 3 (unaffected female)	Childhood	Severe muscle impairment, respiratory distress, early death	700+

**Figure 12.10** Expanding genes explain anticipation. In some disorders, symptoms that worsen from one generation to the next—termed *anticipation*—have a physical basis: The gene is expanding as the number of repeats grows.



## Reading 12.1

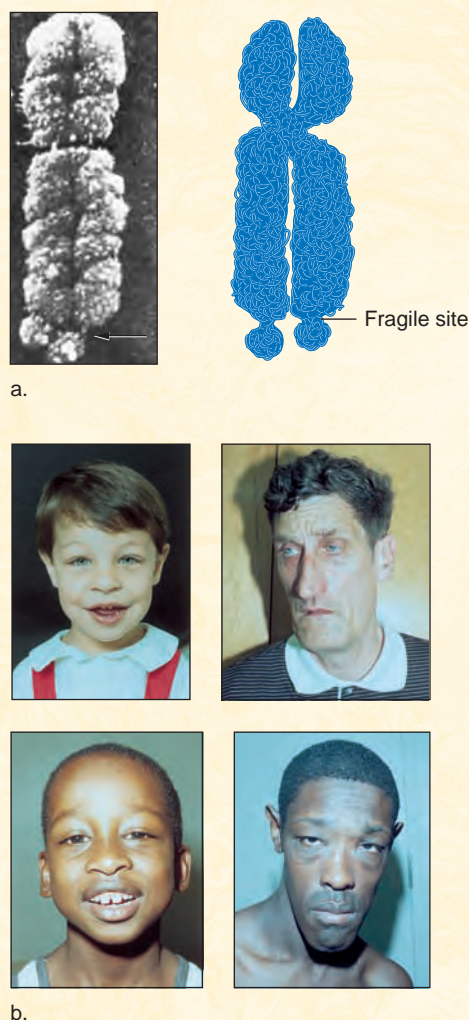
# Fragile X Mutations Affect Boys and Their Grandfathers

In the 1940s, geneticists hypothesized that a gene on the X chromosome confers mental retardation, because more affected individuals are male. It wasn't until 1969, though, that a clue emerged to the genetic basis of X-linked mental retardation. Two retarded brothers and their mother had an unusual X chromosome. The tips at one chromosome end dangled, separated from the rest of each chromatid by a thin thread (**figure 1a**). When grown under specific culture conditions (lacking folic acid), this part of the X chromosome was very prone to breaking—hence, the name fragile X syndrome. Although fragile X syndrome was discovered at the chromosomal level, the cause is a mutation at the DNA level. Worldwide, it affects 1 in 2,000 males, accounting for 4 to 8 percent of all males with mental retardation. One in 4,000 females is affected. They usually have milder cases because of the presence of a second, normal X chromosome.

Youngsters with fragile X syndrome look normal, but by young adulthood, their faces are very long and narrow, with a long jaw and protruding ears. The testicles are very large. Mental impairment and behavioral problems include mental retardation, learning disabilities, repetitive speech, hyperactivity, shyness, social anxiety, a short attention span, language delays, and temper outbursts.

Fragile X syndrome is inherited in an unusual pattern. Because the fragile chromosome is the X, the associated syndrome should be transmitted as any X-linked trait is, from carrier mother to affected son. However, penetrance is incomplete. One-fifth of males who inherit the chromosomal abnormality have no symptoms. But because they pass on the affected chromosome to all their daughters—half of whom have some degree of mental impairment—they are called “transmitting males.” A transmitting male's grandchildren may inherit fragile X syndrome.

A triplet repeat mutation causes fragile X syndrome. In unaffected individuals, the fragile X area contains about 30 repeats of the sequence CGG, in a gene called the fragile X mental retardation gene (*FMR1*). In people who have the fragile chromosome and show its effects, this region is expanded



**Figure 1** Fragile X syndrome. A fragile site on the tip of the long arm of the X chromosome (**a**) is associated with mental retardation and a characteristic long face that becomes pronounced with age (**b**).

to 200 to 2,000 CGG repeats. Transmitting males, as well as females with mild symptoms, or who have affected sons, often have a premutation consisting of 50 to 200 repeats.

The *FMR1* gene encodes fragile X mental retardation protein (FMRP). This protein, when abnormal, binds to and disables several different mRNA molecules whose encoded proteins are crucial for brain neuron function.

Despite our knowledge of the genetic mechanism behind fragile X syndrome, mysteries remain. Recently, a distinct type

of disorder has been described in the maternal grandfathers of boys who have fragile X syndrome. A few years ago, clinicians noticed that mothers of boys with fragile X syndrome very often reported the same symptoms in their fathers—tremors, balance problems, and then cognitive or psychiatric difficulties (inability to plan or pay attention, and inappropriate behaviors). The grandfathers were sometimes misdiagnosed with Parkinson disease due to the tremors. However, Parkinson's patients can pass the “tandem gait test” (walking a straight line) while the grandfathers could not. The grandfathers' symptoms worsen with time and can lead to premature death (**table 1**).

Further investigation led to the description of the new condition, called fragile X-associated tremor/ataxia syndrome (FXTAS, OMIM 300623). (Ataxia refers to poor balance and coordination.) So far the disorder has been studied in a dozen brains obtained after the grandfathers died and in a mouse model. Like the granddads, the mice are fine until middle age. Then they, too, develop tremors and balance problems as well as nervousness and memory impairment. The researchers speculate that the symptoms of FXTAS arise from excess FMR1 mRNA, which attracts and disables other mRNAs.

The discovery of FXTAS has important genetic counseling implications. As neurologists learn to distinguish this disorder from others, such as Parkinson disease, daughters can be counseled that they might pass on the condition to sons, and be offered testing.

**Table 1**

### Prevalence of FXTAS in Grandfathers of Fragile X Syndrome Grandsons

Age	Prevalence
50s	17%
60s	38%
80 <sup>+</sup>	75%



The mechanism behind triplet repeat disorders lies in the DNA sequence. The bases of the repeated triplets implicated in the expansion diseases, unlike others, bond to each other in ways that bend the DNA strand into shapes, such as hairpins. These shapes then interfere with replication, which causes the expansion. Once these repeats are translated, the extra-long proteins shut down cells in various ways:

- binding to parts of transcription factors that have stretches of amino acid repeats similar to or matching the expanded repeat
- blocking proteasomes and thereby enabling misfolded proteins to persist
- directly triggering apoptosis.

Triplet repeat proteins may also enter the nucleus eventhough their wild type versions function only in the cytoplasm, or vice versa.

The triplet repeat disorders are said to cause a “dominant toxic gain of function.” This means that they cause something novel to happen, rather than removing a function, such as is often associated with recessive enzyme deficiencies. The idea of a gain of function arose from the observation that deletions of these genes do not cause symptoms. **Table 12.7** describes

several triplet repeat disorders. Particularly common among them are the “poly-glutamine diseases” that have repeats of the mRNA codon CAG, which encodes the amino acid glutamine.

For some triplet repeat disorders, the mutation thwarts gene expression before a protein is even manufactured. In myotonic dystrophy type 1 the expansion is in the initial untranslated region of a gene on chromosome 19, resulting in a huge mRNA. When genetic testing became available for the disorder, researchers discovered a second form of the illness in people who had wild type alleles for the chromosome 19 gene. They have myotonic dystrophy type 2, which is caused by an expanding *quadruple* repeat of CCTG in a gene on chromosome 3. Affected individuals have more than 100 copies of the repeat, compared to the normal fewer than 10 copies.

When researchers realized that this second repeat mutation for myotonic dystrophy was also in a non-protein-encoding part of the gene—an intron—a mechanism of disease became apparent: The mRNA is not processed normally and as a result cannot exit the nucleus. In myotonic dystrophy type 1, the excess material is added to the start of the gene; in type 2, it appears in an intron that is not excised. The bulky mRNAs bind to a protein that,

in turn, alters intron splicing in several other genes. Deficiency of the proteins encoded by these final affected genes causes the symptoms.

A lesson learned from the expanding repeat disorders is that a DNA sequence is more than just one language that can be translated into another. Whether a sequence is random—CGT CGT ATG CAT CAG, for example—or highly repetitive—such as CAG CAG CAG CAG and on and on—can affect transcription, translation, or the ways that proteins interact.

### Copy Number Variants

Because of the linguistic nature of the human genome—that is, the fact that a sequence of one type of “letter” is transcribed and translated into others—it was logical to think that the only way that people might differ from each other is in the DNA sequence. Identifying mutations and SNPs track these types of differences. But our genomes are also distinguished by differing numbers of *copies* of particular sequences. The way that DNA was sequenced when the human genome was deciphered did not reveal copies, because a particular sequence was only counted once. But copy number is important, and maps of them are now being assembled.

**Table 12.7**  
Triplet Repeat Disorders

Disorder	OMIM	mRNA Repeat	Normal Number of Copies	Disease Number of Copies	Signs and Symptoms (Phenotype)
Fragile X syndrome	309550	CGG or CCG	6–50	200–2,000	Mental retardation, large testicles, long face
Friedreich ataxia	229300	GAA	6–29	200–900	Loss of coordination and certain reflexes, spine curvature, knee and ankle jerks
Haw River syndrome	140340	CAG	7–25	49–75	Loss of coordination, uncontrollable movements, dementia
Huntington disease	143100	CAG	10–34	40–121	Personality changes, uncontrollable movements, dementia
Jacobsen syndrome	147791	CGG	11	100–1,000	Poor growth, abnormal face, slow movement
Myotonic dystrophy type I	160900	CTG	5–37	80–1,000	Progressive muscle weakness; heart, brain, and hormone abnormalities
Myotonic dystrophy type II	602668	CCTG	<10	>100	Progressive muscle weakness; heart, brain, and hormone abnormalities
Spinal and bulbar muscular atrophy	313200	CAG	14–32	40–55	Muscle weakness and wasting in adulthood
Spinocerebellar ataxia (5 types)	271245	CAG	4–44	40–130	Loss of coordination

An English language metaphor is useful for distinguishing point mutations and SNPs from **copy number variants** (CNVs), which are sequences that are present in more than one place in a genome. If a wild type short sequence and a variant with two SNPs are written as:

*The fat rat sat on a red cat* (wild type)  
*The fat rat sat **in** a red **hat*** (two SNPs)

Then the sequence with two copy number variants might be:

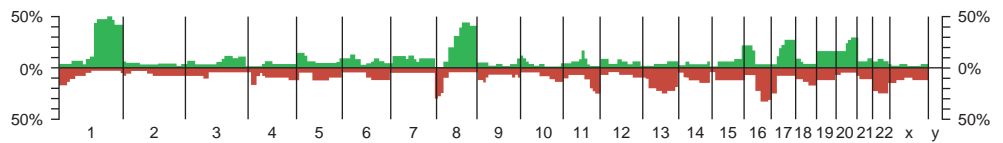
*The **fat fat** rat sat on a **red red red** cat*

Researchers comparing gene copy numbers in populations are finding that copy number variability may be common and may contribute significantly to the differences among us. One of the first such studies searched for extra copies of sequences larger than 1,000 bases (one kilobase, or kb) in approximately 12 percent of the genome, and found about 1,500 regions. This and other studies reveal that a repeated sequence may range in size from a few bases to millions, and copies may lie next to each other on a chromosome or may be part of different chromosomes. Copy number variants therefore bridge the classic DNA and chromosomal levels of mutation, and therefore we encounter them again in chapter 13.

CNVs may have no effect on the phenotype, or they may disrupt a gene's function and harm health. They are not the major cause of mutation—only 5 to 6 percent of known disease-causing mutations include deletions or repeats of a gene. A disruption by a CNV may be direct, such as by inserting into a gene and offsetting the reading frame, or indirect, such as destabilizing surrounding sequences.

Susceptibility to HIV infection is an example of a trait that is affected by the number of copies of a specific gene. The gene *CCL3L1*, which stands for “CC chemokine ligand 3-like 1,” is an immune system molecule that binds the cell surface receptor protein CCR5, mentioned at the start of the chapter. The CCR5 receptor is the entryway into the cell for HIV. If *CCL3L1* blocks the receptor, HIV can't get in and the person does not become infected. Population-level studies have shown that individuals who become infected with HIV, and especially

### Breast Carcinomas



**Figure 12.11** CGH data represent chromosome copy number changes (imbalances).

This figure shows copy number abnormalities in 666 breast cancer cases, with green (up) indicating gains and red (down) indicating losses of genetic material. Nearly half of all analyzed cases had additional copies of sequences in chromosomes 1 and 8, with other frequent gains in chromosomes 16, 17, and 20. Losses frequently were in chromosomes 8, 11, 13, and 16. Some of these regions are known to contain genes that cause cancer.

those with severe, rapidly progressing cases, have the *fewest* copies of the *CCL3L1* gene. In those populations, people not infected with HIV tend to have the *most* copies of the *CCL3L1* gene. Interestingly, it is having the fewest copies in a population that puts a person at risk, not the absolute number. That is, a person with four copies living where most people have two copies is protected, but if she had the same four copies in a population where the average number is eight, she'd be at high risk. This effect isn't understood.

Researchers use a technique called **comparative genomic hybridization** (CGH) to tell, at a glance, when a DNA sequence is present in a genome in more than the normal two copies. CGH compares two sources of DNA, such as from patients with a certain type of cancer and healthy controls. The data are displayed as a series of peaks and valleys along a horizontal line, as **figure 12.11** shows. The *x* axis represents the chromosomes. Areas without peaks or valleys indicate chromosome regions where the copy number is the same in the two groups of DNA samples—which usually means that both groups have the normal two copies of any particular gene. Peaks usually depict regions where DNA from the patients has an extra copy or copies of a sequence, and the valleys are where the patient DNA has lost genetic material. Cancer cells tend to have many such changes.

We still have much to learn about copy number variants. It isn't yet known how common they are, how many there are, how many are correlated to phenotypes (disorders), and what is the range of what we can call a “normal” human genome.

## Key Concepts

1. A point mutation alters a single DNA base and can occur in any part of a gene.
2. In a transversion, a purine replaces a pyrimidine, or vice versa; in a transition, a purine replaces a purine or a pyrimidine replaces a pyrimidine.
3. A missense mutation replaces one amino acid with another.
4. A nonsense mutation changes an amino-acid-coding codon into a “stop” codon, shortening the protein. A stop codon that is changed to an amino-acid-coding codon lengthens the protein.
5. Mutations in intron/exon splice sites, promoters, or other control regions affect gene function.
6. Inserting or deleting bases can cause a frameshift mutation.
7. Tandem duplications repeat a section of a gene.
8. Pseudogenes are nonfunctional sequences very similar to nearby functional genes.
9. Transposons can move, insert into genes, and cause illness.
10. Expanded repeats exert effects that arise from protein misfolding.
11. Copy number variants can affect the phenotype and may play a large role in distinguishing individuals.

## 12.4 The Importance of Position

The degree to which a mutation alters the phenotype depends upon where in the gene the change occurs, and how the mutation affects the conformation, activity, or expression of



an encoded protein. A mutation that replaces an amino acid with a very similar one would probably not affect the phenotype greatly, because it wouldn't substantially change the conformation of the protein. Even substituting a very different amino acid would not have much effect if the change is in part of the protein not crucial to its function. In contrast, mutations in the beta globin gene that critically changed the protein led to the symptoms in the child described in the chapter opener.

The effects of specific mutations are well-studied in hemoglobin. They are less understood, but still fascinating, in the gene that encodes prion protein.

### Globin Variants

Because the globin gene mutations were the first to be analyzed in humans, and because some variants are easily detected using electrophoresis, hundreds of globin gene mutations have been known for years. Mutations in these genes can cause anemia with or without sickling, or cause cyanosis (a blue pallor due to poor oxygen binding). Rarely, a mutation boosts the molecule's affinity for oxygen. Some globin gene variants exert no effect and are thus considered "clinically silent" (Table 12.8).

Oddly, hemoglobin S and hemoglobin C are variants that result from mutations that change the sixth amino acid in the beta globin polypeptide, but in different ways.

Homozygotes for hemoglobin S have sickle cell disease, yet homozygotes for hemoglobin C are healthy. Both types of homozygotes are resistant to malaria because the unusual hemoglobin alters the shapes and surfaces of red blood cells in ways that keep out the parasite that causes the illness, discussed in chapter 15.

An interesting consequence of certain mutations in either the alpha or beta globin chains is hemoglobin M. Normally, the iron in hemoglobin is in the ferrous form, which means that it has two positive charges. In hemoglobin M, the mutation stabilizes the ferric form, which has three positive charges and cannot bind oxygen. Fortunately, an enzyme converts the abnormal ferric iron to the normal ferrous form, so that the only symptom is usually cyanosis. The condition has been known for more than two hundred years in a small town in Japan. Many people there have "blackmouth" because of the cyanosis caused by the faulty hemoglobin. It is autosomal dominant.

Even more noticeable than people with blackmouth are the "blue people of Troublesome Creek". Seven generations ago, in 1820, a French orphan named Martin Fugate who settled in this area of Kentucky brought in a recessive gene that causes a form of methemoglobinemia. He was missing an enzyme (cytochrome b5 reductase) that normally catalyzes a reaction that converts a type of hemoglobin with poor oxygen affinity, called methemoglobin, back into normal hemoglobin

by adding an electron. Martin's wife was a carrier for this very rare disease. After extensive inbreeding in the isolated community—their son married his aunt, for example—a large pedigree of "blue people" of both sexes arose.

In "blue person disease," the excess oxygen-poor hemoglobin causes a dark blue complexion. Carriers may have frighteningly bluish lips and fingernails at birth, which usually improve. This form of methemoglobinemia also affects the Navajo and Eskimos. Treatment is simple: A tablet of methylene blue, a commonly used dye, adds the electron back to methemoglobin, converting it to normal hemoglobin.

### Susceptibility to Prion Disorders

For the prion protein gene, as with the globin genes, certain mutations exert drastic effects, while others do not. Recall from chapter 10 that a prion is a protein that assumes both stable and infectious conformations. A prion disease can be inherited, such as fatal familial insomnia, or acquired, such as developing variant Creutzfeldt-Jakob disease from eating beef from a cow that had bovine spongiform encephalopathy ("mad cow disease"). The prion protein has at least eight distinct conformations. The normal form of the protein has a central core made up of helices. In a disease-causing form, the helices open into a sheet. Precise

**Table 12.8**  
**Globin Mutations**

Associated Phenotype	Name	Mutation
Clinically silent	Hb Wayne	Single-base deletion in alpha gene causes frameshift, changing amino acids 139–141 and adding amino acids
	Hb Grady	Nine extra bases add three amino acids between amino acids 118 and 119 of alpha chain
Oxygen binding	Hb Chesapeake	Change from arginine to leucine at amino acid 92 of beta chain
	Hb McKees Rocks	Change from tyrosine to STOP codon at amino acid 145 in beta chain
Anemia	Hb Constant Spring	Change from STOP codon to glutamine elongates alpha chain
	Hb S	Change from glutamic acid to valine at amino acid 6 in beta chain causes sickling
Protection against malaria	Hb Leiden	Amino acid 6 deleted from beta chain
	Hb C	Change from glutamic acid to lysine at amino acid 6 in beta chain causes sickling

genetic changes control the plasticity of the prion protein. The 129th amino acid is particularly important. In people who inherit prion disorders, amino acid 129 is either valine in all copies of the protein (genotype VV, causing the insomnia) or methionine in all copies (genotype MM, causing a form of Creutzfeldt-Jakob disease). These people are homozygous for this small part of the gene. Most people, however, are heterozygous, with valine in some prion proteins and methionine in others (genotype VM). Perhaps having two different amino acids at this position enables the proteins to assemble and to carry out their normal functions without damaging the brain.

A mutation at a different site in the prion protein gene raises the risk of brain disease even higher. Normally prion protein folds so that amino acid 129 is near amino acid 178, which is aspartic acid. People who inherit prion diseases are homozygous for the gene at position 129, and have another mutation that changes amino acid 178 to asparagine.

## Key Concepts

1. Whether a mutation alters the phenotype, and how it does so, depends upon where in the protein the change occurs.
2. Mutations in globin genes may cause anemia or cyanosis, or they may be silent. Hemoglobin M affects the ability of the iron to bind oxygen.
3. Mutations in two parts of the prion protein gene predispose to developing a prion disorder.

## 12.5 Factors That Lessen the Effects of Mutation

Mutation is a natural consequence of DNA's ability to change. This flexibility is essential for evolution because it generates new variants, some of which may resist environmental change and enable a population or even a species to survive. However, many factors minimize the deleterious effects of mutations on phenotypes.

The genetic code imparts built-in protection against mutation. Synonymous codons render many alterations in the third

codon position "silent." For example, a change from RNA codon CAA to CAG does not alter the designated amino acid, glutamine, so a protein whose gene contains the change would not be altered. Other genetic code nuances prevent synthesis of drastically altered proteins. For example, mutations in the second codon position sometimes replace one amino acid with another that has a similar conformation, minimizing disruption of the protein's form. GCC mutated to GGC, for instance, replaces alanine with equally small glycine.

A **conditional mutation** affects the phenotype only under certain conditions. This can be protective if an individual avoids the exposures that trigger symptoms. Consider a common variant of the X-linked gene that encodes glucose 6-phosphate dehydrogenase (G6PD), an enzyme that immature red blood cells use to extract energy from glucose. One hundred million people worldwide have G6PD deficiency (OMIM 305900), which can cause life-threatening hemolytic anemia, but only under rather unusual conditions—eating fava beans, inhaling pollen in Baghdad, or taking a certain antimalarial drug.

In the fifth century B.C., the Greek mathematician Pythagoras wouldn't allow his followers to consume fava beans—he had discovered that it would sicken some of them. During the Second World War, several soldiers taking the antimalarial drug primaquine developed hemolytic anemia. A study began shortly after the war to investigate the effects of the drug on volunteers at the Stateville Penitentiary in Joliet, Illinois. Researchers identified abnormal G6PD in people who developed anemia when they took the drug.

What do fava beans, antimalarial drugs, and dozens of other triggering substances have in common? They "stress" red blood cells by exposing them to oxidants, chemicals that strip electrons from other compounds. Without the enzyme, the stress bursts the red blood cells.

Another protection against mutation occurs in stem cells. When a stem cell divides to yield another stem cell and a progenitor or differentiated cell, the oldest DNA strands segregate with the stem cell, and the most recently replicated DNA strands go to the more specialized daughter cells. This makes sense in organs where stem cells very actively yield specialized daughter cells, such as the

skin and small intestine. Because mutations occur when DNA replicates, this skewed distribution of chromosomes sends the DNA most likely to harbor mutations into cells that will soon be shed (from a towel rubbed on skin or in a bowel movement) while keeping mutations away from the stem cells that must continually regenerate the tissues.

## Key Concepts

1. Genetic code degeneracy ensures that some third-codon-position mutations do not alter the specified amino acid. Changes in the second codon position often substitute a structurally similar amino acid.
2. Conditional mutations are expressed only in certain environments.
3. Preferential segregation of the oldest DNA strands to stem cells rather than daughter cells protects against mutation.

## 12.6 DNA Repair

Any manufacturing facility tests a product in several ways to see whether it has been assembled correctly. Mistakes in production are rectified before the item goes on the market—at least, most of the time. The same is true for a cell's manufacture of DNA.

Damage to DNA becomes important when the genetic material is replicated. In response to damage, the cell may die by apoptosis or it may repair the error. If the cell doesn't die or the error is not repaired, cancer may result. Fortunately, DNA replication is incredibly accurate—only 1 in 100 million or so bases is incorrectly incorporated. DNA polymerase as well as **DNA damage response** genes encode repair enzymes that oversee the accuracy of replication. The DNA damage response consists of a cell's detecting damage and signaling systems in the cell that carry out responses (death or repair). More than 50 DNA damage response genes have been identified.

All eukaryotes can repair their nuclear DNA, although some species do so more efficiently than others. Mitochondrial DNA cannot repair itself, which accounts for its higher mutation rate. The master at DNA repair is a large, reddish microbe.

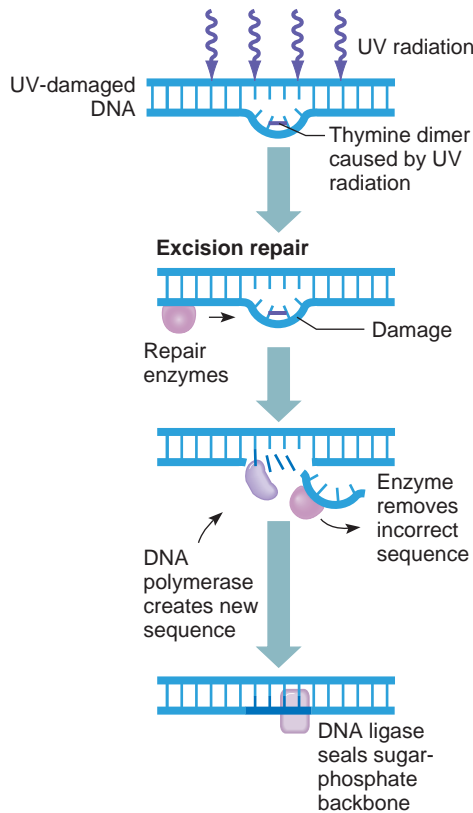
*Deinococcus radiodurans* was discovered in a can of spoiled ground meat at the Oregon Agricultural Experiment Station in Corvallis in 1956, where it had withstood radiation used to sterilize the food. It tolerates 1,000 times the radiation level that a person can, and it can even live amidst the intense radiation of a nuclear reactor. The bacterium realigns its radiation-shattered pieces of DNA. Then enzymes bring in new nucleotides and assemble the pieces.

The discovery of DNA repair systems began with observations in the late 1940s that when fungi were exposed to ultraviolet (UV) radiation, those cultures later placed nearest a window grew best. The researchers who noted these effects were not investigating DNA repair, but were using UV light in other experiments. Therefore, DNA repair was inadvertently discovered before the structure of DNA was. The DNA-damaging effect of UV radiation, and the ability of light to correct it, was soon observed in a variety of organisms. (UV radiation has a shorter wavelength than visible light. They are both types of electromagnetic radiation.)

## Types of DNA Repair

Since its beginning, the Earth has been periodically bathed in UV radiation. Volcanoes, comets, meteorites, and supernovas all depleted ozone in the atmosphere, which allowed ultraviolet wavelengths of light to reach organisms. The shorter wavelengths—UVA—are not dangerous, but the longer UVB wavelengths damage DNA by forming an extra covalent bond between adjacent (same-strand) pyrimidines, particularly thymines (**figure 12.12**). The linked thymines are called thymine dimers. Their extra bonds kink the double helix sufficiently to disrupt replication and permit insertion of a noncomplementary base. For example, an A might be inserted opposite a G or C, instead of opposite a T. Thymine dimers also disrupt transcription.

Early in the evolution of life, organisms that could survive UV damage had an advantage. Enzymes enabled them to do this, and because enzymes are gene-encoded, DNA repair came to persist. In many modern species, three types of DNA repair peruse the genetic material for mismatched base pairs. In the first type, enzymes called photolyases absorb energy



**Figure 12.12** Excision repair.

Human DNA damaged by UV light is repaired by excision repair, which removes and replaces the pyrimidine dimer and a few surrounding bases.

from visible light and use it to detect and bind to pyrimidine dimers, then break the extra bonds. This type of repair, called photo-reactivation, enables UV-damaged fungi to recover from exposure to sunlight. Humans do not have this type of DNA repair.

In the early 1960s, researchers discovered a second type of DNA self-mending, called **excision repair**, in mutant *E. coli* that were unable to repair UV-induced DNA damage. Enzymes cut the bond between the DNA sugar and base and snip out—or excise—the pyrimidine dimer and surrounding bases (see figure 12.12). Then, a DNA polymerase fills in the correct nucleotides, using the exposed template as a guide. DNA polymerase also detects and corrects mismatched bases in newly replicated DNA.

Humans have two types of excision repair. **Nucleotide excision repair** replaces up to 30 nucleotides and removes errors that result from several types of insults, including exposure to chemical carcinogens, UVB in sunlight, and oxidative damage.

Thirty different proteins carry out nucleotide excision repair, functioning together as a structure called a **repairoosome**. The second type of excision repair, **base excision repair**, replaces one to five nucleotides at a time, but specifically corrects errors that result from oxidative damage. Oxygen free radicals are highly reactive forms of oxygen that arise during chemical reactions such as those of metabolism and transcription. Free radicals damage DNA. Genes that are very actively transcribed face greater oxidative damage from free radicals; base excision repair targets this type of damage.

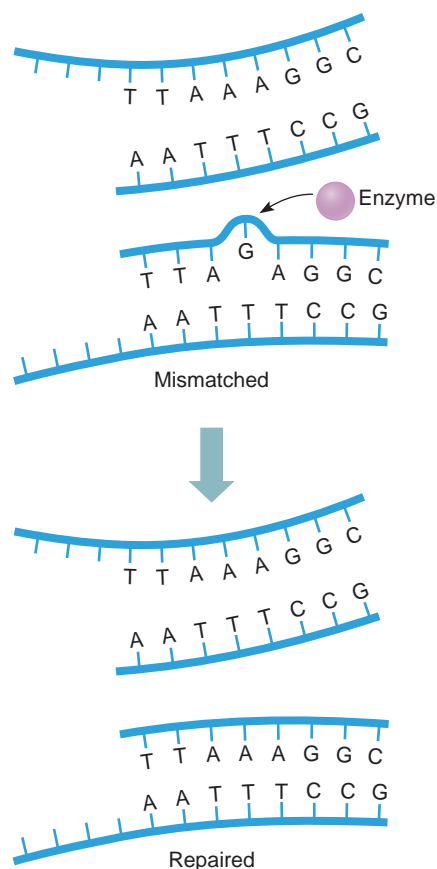
A third mechanism of DNA sequence correction is **mismatch repair**. Enzymes “proofread” newly replicated DNA for small loops that emerge from the double helix. The enzymes excise the mismatched base so that it can be replaced (**figure 12.13**). These loops emerge from where the two strands do not precisely align, but instead slip and misalign. This occurs where very short DNA sequences repeat. These sequences, called **microsatellites**, are scattered throughout the genome. Like minisatellites, microsatellite lengths can vary from person to person, but within an individual, they are usually the same length. Excision and mismatch repair differ in the cause of the error—UV-induced pyrimidine dimers versus replication errors—and in the types of enzymes involved.

The three forms of DNA repair in human cells relieve the strain on thymine dimers or replace incorrectly inserted bases. Another form of repair can heal a broken sugar-phosphate backbone in both strands, which can result from exposure to ionizing radiation or oxidative damage. This type of insult breaks a chromosome, which can cause cancer. At least two types of multiprotein complexes reseal the sugar-phosphate backbone, either by rejoining the broken ends or recombining with DNA on the unaffected homolog.

In yet another type of DNA repair called **damage tolerance**, a “wrong” DNA base is left in place, but replication and transcription proceed. “Sloppy” DNA polymerases, with looser adherence to the base-pairing rules, read past the error, randomly inserting any other base. It is a little like retaining a misspelled word in a sentence—usually the meaning remains clear.

**Figure 12.14** summarizes DNA repair mechanisms.

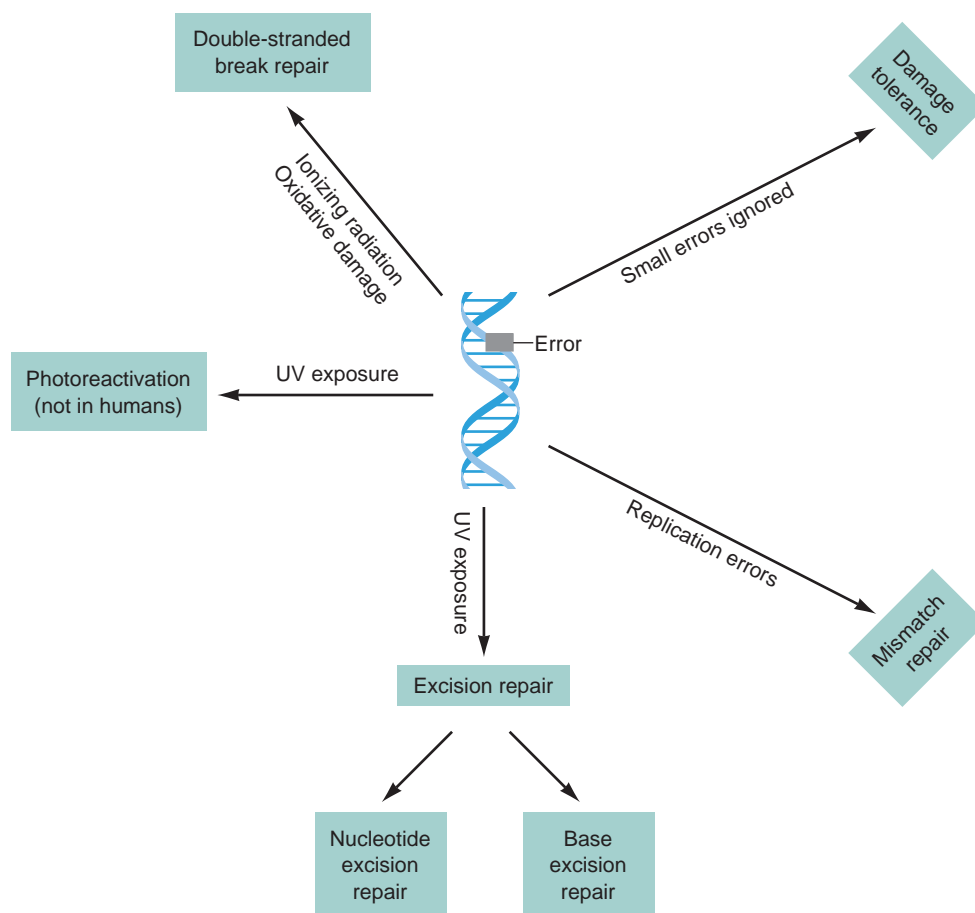




**Figure 12.13 Mismatch repair.** In this form of DNA repair, enzymes detect loops and bulges in newly replicated DNA that indicate mispairing. The enzymes correct the error. Highly repeated sequences are more prone to this type of error.

## DNA Repair Disorders

The ability to repair DNA is crucial to health. Mutations in any of the DNA damage response genes can cause disorders. If both copies of a repair gene are mutant, a disorder can result. Heterozygotes (carriers) who have one mutant repair gene may be more sensitive to damage from environmental toxins. A well-studied DNA damage response gene encodes a protein called p53. It controls whether DNA is repaired and the cell salvaged, or the cell dies by apoptosis. Signal transduction activates p53 protein, stabilizing it and causing it to aggregate into complexes consisting of four proteins. These quartets bind DNA at four palindromic repeats that indicate genes that slow the cell cycle. The cycle must slow for repair to take place. If the damage is too severe, the p53 protein quartets instead increase the



**Figure 12.14 DNA repair mechanisms.**

rate of transcription of genes that promote apoptosis.

In DNA repair disorders, chromosome breakage caused by factors such as radiation cannot be repaired. Mutations in repair genes therefore greatly increase susceptibility to certain types of cancer following exposure to ionizing radiation or chemicals that affect cell division. These conditions develop because errors in the DNA sequence accumulate and are perpetuated to a much greater extent than they are in people with functioning repair systems. We conclude this chapter with a closer look at repair disorders, which are very rare.

### Trichothiodystrophy (OMIM 601675)

At least five genes can cause trichothiodystrophy. At its worst, this condition causes dwarfism, mental retardation, and failure to develop, in addition to scaly hair with low sulfur content. Although the child may

appear to be normal for a year or two, growth soon slows dramatically, signs of premature aging begin, and life ends early. Hearing and vision may fail. Interestingly, the condition does not increase the risk of cancer. Symptoms reflect accumulating oxidative damage. Individuals have faulty nucleotide excision repair, base excision repair, or both.

### Inherited Colon Cancer

Hereditary nonpolyposis colon cancer (HNPCC) (OMIM 120435) was linked to a DNA repair defect when researchers discovered different-length microsatellites within an individual. Because mismatch repair normally keeps a person's microsatellites all the same length, people with this type of colon cancer might have a breakdown in this form of DNA repair. The causative gene is located on chromosome 2 and is remarkably similar to a corresponding mismatch repair gene in *E. coli*. HNPCC is common, affecting 1 in 200 people.

## Xeroderma Pigmentosum (XP) (OMIM 278700)

A child with XP must stay indoors in artificial light, because even the briefest exposure to sunlight causes painful blisters. Failing to cover up and use sunblock can result in skin cancer (**figure 12.15**). More than half of all children with XP develop the cancer before they reach their teens. People with XP have a 1,000-fold increased risk of developing skin cancer compared to others, and a 10-fold increase in the risk of developing internal tumors.

XP is autosomal recessive, and results from mutations in any of seven genes. It can reflect malfunction of nucleotide excision repair or deficient “sloppy” DNA polymerase, both of which allow thymine dimers to stay and block replication. Only about 250 people in the world are known to have XP. A family living in upstate New York runs a special summer camp for children with XP, where they turn night into day. Activities take place at night, or in special areas where the



**Figure 12.15 A DNA repair disorder.** The marks on this child's face result from sun exposure. He is highly sensitive because he has inherited xeroderma pigmentosum (XP), an impairment of excision repair. The large lesion on his chin is a skin cancer.

windows are covered and light comes from low-ultraviolet incandescent lightbulbs.

## Ataxia Telangiectasis (AT) (OMIM 208900)

This multisymptom disorder is the result of a defect in a kinase that functions as a cell cycle checkpoint (see figure 2.15). In AT, cells proceed through the cell cycle without pausing just after replication to inspect the new DNA and to repair any mispaired bases. Some cells die through apoptosis if the damage is too great to repair. Because of the malfunctioning cell cycle, individuals who have this autosomal recessive disorder have 50 times the risk of developing cancer, particularly of the blood. About 40 percent of individuals with ataxia telangiectasis have cancer by age 30. Additional symptoms include poor balance and coordination (ataxia), red marks on the face (telangiectasia), delayed sexual maturation, and high risk of contracting lung infections and developing diabetes mellitus. These symptoms probably arise from disruption of other functions of the kinase.

AT is rare, but heterozygotes are not. They make up from 0.5 to 1.4 percent of various populations. Carriers may have mild radiation sensitivity, which causes a two- to sixfold increase in cancer risk over the general population. People who know they are AT carriers should question suggested dental or medical X rays, because for them even low exposure may cause cancer.

DNA's changeability, so vital for evolution of a species, comes at the cost of occasional harm to individuals. Each of us harbors a few mutations, and several polymorphisms, although most are hidden in the recessive state. Individuals whose mutations cause illness or deformity can face hardships, both medical and due to discrimination. Perhaps we can learn from the ancient Egyptians, who honored people who were genetically different (**figure 12.16**).

The dry air of ancient Egypt and the meticulous recording of daily life in art and burial places reveal that people with short stature, particularly those with autosomal dominant achondroplasia (a form of dwarfism), were accepted, important, and even revered as gods. Ancient Egyptian “little people” were jewelers, animal keepers, enter-



**Figure 12.16 The ancient Egyptians accepted and honored people with hereditary dwarfism.** This is the Egyptian dwarf god Bes.

tainers, and personal attendants, often to royalty. High-ranking dwarfs were given special burial places near the pyramids. Wrote Chahira Kozma, a professor of pediatrics at Georgetown University who studies how the ancient Egyptians regarded unusual people, “Dwarfs were accepted in ancient Egypt; their recorded daily activities suggest assimilation into daily life, and their disorder was not shown as a physical handicap. Wisdom writings and moral teachings in ancient Egypt commanded respect for dwarfs and other individuals with disabilities.”

## Key Concepts

1. Many genes encode enzymes that locate and correct errors in replicating DNA, in the DNA damage response.
2. A common cause of noncomplementary base insertion is a UV-induced pyrimidine dimer.
3. Photoreactivation or excision repair can unlink pyrimidine dimers.
4. Mismatch repair corrects noncomplementary base pairs that are inserted into newly replicated DNA.
5. Repair seals broken sugar-phosphate backbones.
6. DNA damage tolerance allows replication to proceed past a mismatched base.
7. Abnormal repair genes cause disorders usually associated with chromosome breaks and predisposition to cancer.

# Summary

## 12.1 Mutations Can Alter Proteins—Three Examples

1. A **mutation** is a change in a gene's nucleotide base sequence that affects less than 1 percent of a population and can cause a **mutant** phenotype. A polymorphism is more common and may not alter the phenotype.
2. A **germline mutation** originates in meiosis and affects all cells of an individual. A **somatic mutation** originates in mitosis and affects a subset of cells.
3. A mutation disrupts the function or amount of a protein or introduces a new function. Loss-of-function mutations are usually recessive, and altered or new-function mutations are dominant. Whether different mutations in a gene cause the same or distinct illnesses varies; nomenclature is inconsistent.

## 12.2 Causes of Mutation

4. A spontaneous mutation arises due to chemical phenomena or to an error in DNA replication. Spontaneous mutation rate is characteristic of a gene and is more likely to occur in repeated or symmetrical DNA sequences.
5. **Mutagens** are chemicals or forms of radiation that can induce mutation by deleting, substituting, or adding bases. An organism may be exposed to a mutagen intentionally, accidentally, or naturally.

## 12.3 Types of Mutations

6. A **point mutation** alters a single DNA base. It may be a **transition** (purine to purine or pyrimidine to pyrimidine) or a

**transversion** (purine to pyrimidine or vice versa). A **missense mutation** substitutes one amino acid for another, while a **nonsense mutation** substitutes a “stop” codon for a codon that specifies an amino acid, shortening the protein product. Point mutations in splice sites can lead to many extra or missing amino acids.

7. Adding or deleting genetic material may upset the reading frame or otherwise alter protein function.
8. A pseudogene results when a duplicate of a gene mutates. It may disrupt chromosome pairing, causing mutation.
9. Transposons may disrupt the functions of genes they jump into.
10. Expanding triplet repeat mutations add stretches of the same amino acid to a protein. They expand because they attract each other, which affects replication. This type of mutation may add a function, often leading to a neurodegenerative disease when the number of repeats exceeds a threshold level.
11. **Copy number variants** may have no effect on phenotype, may directly cause disease, or may indirectly cause disease.

## 12.4 The Importance of Position

12. Several types of mutations can affect a gene.
13. Mutations in the globin genes may affect the ability of the blood to transport oxygen, or they may have no effect.
14. Susceptibility to prion disorders requires two mutations that affect different parts of the protein that interact as the amino acid chain folds.

## 12.5 Factors That Lessen the Effects of Mutation

15. Synonymous codons limit the effects of mutation. Changes in the second codon position often substitute a similarly shaped amino acid.
16. **Conditional mutations** are expressed only in response to certain environmental triggers.
17. Sending the most recently replicated DNA into cells headed for differentiation, while sending older strands into stem cells, protects against mutation.

## 12.6 DNA Repair

18. DNA polymerase proofreads DNA, but repair enzymes correct errors in other ways.
19. Photoreactivation repair uses light energy to split pyrimidine dimers.
20. In **excision repair**, pyrimidine dimers are removed and the area filled in correctly. **Nucleotide excision repair** replaces up to 30 nucleotides from various sources of mutation. **Base excision repair** fixes up to five bases that paired incorrectly due to oxidative damage.
21. **Mismatch repair** proofreads newly replicated DNA for loops that indicate noncomplementary base pairing.
22. DNA repair also fixes the sugar-phosphate backbone. Damage tolerance enables replication to continue beyond a mismatch.
23. Mutations in repair genes break chromosomes and increase cancer risk.

# Review Questions

1. How do a “silent mutation” and a polymorphism that is a “harmless variant” differ?
2. How does a point mutation differ from a SNP, and how are they similar?
3. Distinguish between a germline and a somatic mutation. Which is likely to be more severe? Which can be transmitted to offspring?
4. Why is the collagen molecule especially likely to be altered by mutation?
5. What criteria should be used to determine whether mutations in a gene are likely to cause different disorders or differing degrees of the same disorder?
6. How can DNA spontaneously mutate?
7. Compare the effects of alpha, beta, and gamma radiation on the human body.
8. What is the physical basis of a mutational hot spot?
9. List two types of mutations that can alter the reading frame.
10. List four ways that DNA can mutate without affecting the phenotype.
11. Cite two ways a jumping gene can disrupt gene function.
12. What is a molecular explanation for the worsening of an inherited illness over generations?
13. Compare and contrast how short repeats within a gene, long triplet repeats within a gene, and repeated genes can cause disease.



14. How does a copy number variant differ from a missense mutation?
15. Why can a mutation that retains an intron's sequence and a triplet repeat mutation have a similar effect on a gene's encoded protein?
16. Why is there not "a" human genome, but many?
17. Cite three ways in which the genetic code protects against the effects of mutation.
18. What is a conditional mutation?
19. How do excision and mismatch repair differ?
20. In trichothiodystrophy, brittle hair and nails and scaly skin arise in some patients only during periods of fever that persist long enough for hair, nail, and skin changes to become noticeable. What type of mutation causes this disorder?
21. Explain how semiconservative DNA replication makes it possible for stem cells to receive the DNA least likely to bear mutations.
22. Consult the genetic code (table 10.5).
  - a. Describe a point mutation (a change of one codon into another) that would not affect a protein's primary structure.
  - b. Look up amino acid structures and identify a point mutation that could drastically alter a protein.

## Applied Questions

1. Consider the following sequence of part of an mRNA molecule:  
 AUGUUGUCAAAAGCAUGGCGGCCA  
 Introduce the following changes to the sequence, and indicate the effect, if any, on the encoded amino acid sequence:
  - a. a missense mutation
  - b. a nonsense mutation
  - c. a frameshift mutation
  - d. a silent mutation
  - e. a transversion
  - f. a transition
  - g. a tandem duplication
  - h. a deletion
2. Retinitis pigmentosa causes night blindness and loss of peripheral vision before age 20. A form of X-linked retinitis pigmentosa (OMIM 300455) is caused by a frameshift mutation that deletes 199 amino acids. How can a simple mutation have such a drastic effect?
3. One form of Ehlers-Danlos syndrome (not the "stretchy skin" type described in the chapter) can be caused by a mutation that changes a C to a T. This change results in the formation of a "stop" codon and premature termination of procollagen. Consult the genetic code (table 10.5) and suggest one way that this can happen.
4. Part of the mRNA sequence of an exon of a gene that encodes a blood protein is:  
 AUGACUCAUCGCGUGUAGUUUACGA  
 Consult table 10.5 to answer the following questions:
  - a. What is the sequence of amino acids that this mRNA encodes?
  - b. What is the sequence if a point mutation changes the tenth base from a C to an A?
  - c. What is the effect of a point mutation that changes the fifteenth base from a U to an A?
  - d. How does the encoded amino acid sequence change if a C is inserted between the fourth and fifth bases?
  - e. Which would be more devastating to the encoded amino acid sequence, insertion of three bases in a row, or insertion of two bases in a row?
5. Susceptibility to developing prion diseases entails a mutation from aspartic acid (*asp*) to asparagine (*asn*). Which nucleotide base changes make this happen?
6. Two teenage boys meet at a clinic to treat muscular dystrophy. The boy who is more severely affected has a two-base insertion at the start of his dystrophin gene. The other boy has the same two-base insertion but also has a third base inserted a few bases away. Explain why the second boy's illness is milder.
7. About 10 percent of cases of amyotrophic lateral sclerosis (also known as ALS and Lou Gehrig disease) are inherited. This disorder causes loss of neurological function over a five-year period. Two missense mutations cause ALS. One alters the amino acid asparagine (*asn*) to lysine (*lys*). The other changes an isoleucine (*ile*) to a threonine (*thr*). List the codons involved and describe how single-base mutations alter the amino acids they specify.
8. In one family, Tay-Sachs disease stems from a four-base insertion, which changes an amino-acid-encoding codon into a "stop" codon. What type of mutation is this?
9. Epidermolytic hyperkeratosis (OMIM 607602) is an autosomal dominant condition that produces scaly skin. It can be caused by a missense mutation that substitutes a histidine (*his*) amino acid for an arginine (*arg*). Write the mRNA codons that could account for this change.
10. A point mutation in the gene *CRYBA4* (OMIM 123631) replaces a phenylalanine codon with a serine codon. The gene encodes  $\beta$ -crystalline protein. In a healthy eye, the proteins align like panes of glass in a greenhouse, sculpting the lens through which light passes. When the gene is mutant, the panes cannot align, and vision is impaired. Consult the genetic code (table 10.5), and suggest two ways that a point mutation can account for this amino acid substitution.
11. Aniridia (OMIM 106200) is an autosomal dominant eye condition in which the iris is absent. In one family, an 11-base insertion in the gene causes a very short protein to form. What kind of mutation must the insertion cause?
12. A biotechnology company has encapsulated DNA repair enzymes in fatty bubbles called liposomes. Why would this be a valuable addition to a suntanning lotion?
13. Keratin-14 is a protein that is built of a helical rod and a head region. Mutation in part of the gene that specifies the helical rod causes epidermolysis bullosa simplex (OMIM 131800), in which skin easily blisters. Mutation in part of the gene that specifies the head region of the protein causes Naegeli-Franceschetti-Jadassohn syndrome (OMIM 161000), which produces several symptoms, including absence of fingerprints, decreased sweating, skin blisters, underdeveloped nails, and defective tooth enamel. Are the disorders that result from mutation in the keratin-14 gene more consistent with the

cystic fibrosis gene, the beta globin gene, or the collagen genes? Cite a reason for your answer.

14. Mutations in one part of the *SCN9A* gene, which encodes a sodium channel receptor protein on certain nerves, cause two types of pain disorders. Paroxysmal extreme pain disorder (OMIM 167400) causes severe, sudden burning pain in the rectum, eyes, and jaw. Mutations that cause this disorder prevent the sodium channels from closing in time, overstimulating the nerves and causing intense pain in the body parts that the nerves serve. In primary erythralgia (OMIM 133020), the arms and legs hurt after exercise or exposure to a rapid outside temperature change. Mutations that cause this disorder make the same receptors more sensitive to stimuli. Are the disorders that result from mutation in the *SCN9A* gene more consistent with the cystic fibrosis gene, the beta globin gene, or the collagen genes? Cite a reason for your answer.

## Web Activities

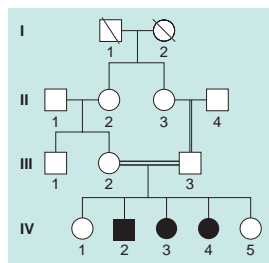
Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 12**, and **Web Activities** to find the website links needed to complete the following activity.

15. Children with Hutchinson-Gilford progeria syndrome age extremely rapidly. In 2003, researchers identified the gene that encodes lamin A as the cause of the disorder. In 18 of 20 children whose DNA was sequenced, a single base change alters a C to a T, but this mutation removes 50 amino acids from the encoded protein. In all 20 children, the parents do not have the mutation.
  - a. Is the mutation in the 18 children *de novo* or induced? What is the evidence for this distinction?
  - b. How can a change in a single base remove 50 amino acids?
  - c. Using OMIM, list and describe six other disorders caused by mutation in the *lamin A* gene.
16. At [www.progenetix.de](http://www.progenetix.de), look at the CGH profiles for various cancers. Select one type, and list three chromosome regions where DNA sequences differ in copy number.
17. Go to [http://www.lpaonline.org/resources\\_faq.html](http://www.lpaonline.org/resources_faq.html) and read the Little People of America's Position Statement on Genetic Discoveries in Dwarfism. Cite an application of genetic testing for achondroplasia that

could be construed as beneficial, and one that could be thought of as harmful.

## Case Studies and Research Results

18. Jan and Marcia meet at a clinic for college students who have cystic fibrosis. They are both studying genetics, and they become interested in learning about the particular mutations in their families. Jan's mutation results in exon skipping. Marcia's mutation is a nonsense mutation. Which young woman probably has more severe symptoms? Cite a reason for your answer.
19. Marshall and Angela have skin cancer resulting from xeroderma pigmentosum. They meet at an event for teenagers with cancer. However, their mutations affect different genes. They decide to marry but not to have children because they believe that each child would have a 25 percent chance of inheriting XP because it is autosomal recessive. Are they correct? Why or why not?
20. For several disorders, copy number variants represent a small fraction of patients (that is, other types of mutations cause most cases). For any of the following such disorders, describe the copy number variant mutation or any other causative mutation by consulting OMIM:
  - a. DiGeorge syndrome
  - b. Williams-Beuren syndrome
  - c. spinal muscular atrophy (any type)
  - d. schizophrenia
  - e. Smith-Magenis syndrome
  - f. Prader-Willi syndrome
  - g. Angelman syndrome
  - h. nephronohthisis
  - i.  $\beta$ -crystalline cataracts
  - j. psoriasis
21. Two girls and a boy in a Pakistani family have a form of deafness caused by a mutation in the gene that encodes a protein called tricellulin (OMIM 610153). The normal protein attaches epithelial (lining) cells in groups of three in the inner ear in a way that establishes compartments whose fluid content differences are crucial to hearing. Below is a pedigree for the family.



- a. What is the mode of inheritance for this form of deafness, and how do you know this?
- b. This form of deafness is rare worldwide, but more common among Pakistani families, many of whose pedigrees have double horizontal lines like the parents in the third generation of this pedigree. What does the double line mean, and how does it account for the increased prevalence of this form of deafness in the population?
- c. The affected children have the following partial sequence for the tricellulin gene: C T G C A A T G T. Unaffected family members have the corresponding sequence of C T G C A G T G T. What are the amino acid differences encoded in these sequences?
22. Presenilin 1 is one of the genes that, when mutant, causes familial Alzheimer disease. The gene is expressed in the heart, and certain mutations cause a condition called dilated cardiomyopathy that leads to heart failure. In the Esposito family, all of the relatives who have or had heart failure have the following partial sequence for the presenilin 1 gene: G A T G A T G G C G G G. Family members with healthy hearts have the sequence G A T G G T G G C G G G. How do the encoded amino acid sequences differ between the healthy and sick family members for this part of the gene?
23. At the Center for Applied Genomics at the Children's Hospital of Philadelphia, 100,000 young children will have their genomes scanned for copy number variants. Researchers plan to compare the resulting CNV profiles with multifactorial disorders that the children have, such as asthma, obesity, cancers, and diabetes, to determine whether copy number variation is important to health. The idea is that the children are so young that environmental influences are minimized, compared, for example, to people who have asthma but have smoked or lived with pollution. Explain how this project might be helpful and how it might be harmful.

# A Second Look

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1. Is each of Juanita's mutations a missense or a nonsense mutation?
2. How would an electrophoresis test on Juanita's father's blood differ from test results from her mother's blood?
3. Which of Juanita's beta globin gene variants is the result of spontaneous mutation, and how do you know this?

Learn to apply the skills of a genetic counselor with additional cases found in the *Case Workbook in Human Genetics*:

Bloom syndrome  
DNA repair  
Gyrate atrophy  
Open-angle glaucoma  
Otospondylomegalaphyseal dysplasia  
Tay-Sachs disease  
von Willebrand disease



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.





# CHAPTER

# 13

## Chromosomes

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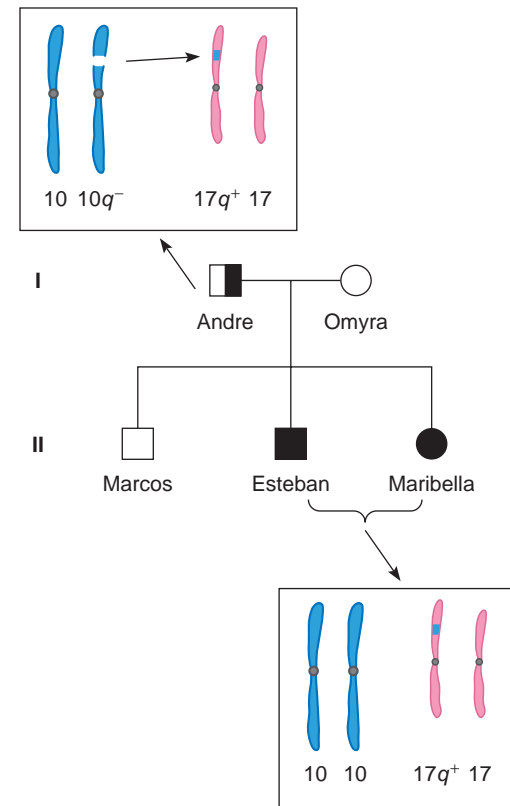
#### 13.5 Uniparental Disomy—A Double Dose from One Parent

### A LATE DIAGNOSIS

Esteban was 17 years old when he learned that he had an unusual chromosome. The discovery explained a lot.

As a baby and toddler, Esteban had been much slower in reaching milestones, such as walking and talking, than his brother Marcos. When he started school, problems emerged: he was learning disabled and had difficulty interacting with others. Esteban had to repeat the third grade so that he could learn to read. He was also very tall and thin, causing teachers to think he was older than he really was and therefore to expect more of him. Still, Esteban was able to learn in regular classrooms with weekly visits to a resource room, and he made a few friends.

Esteban's mother, Omyra, became pregnant when Esteban was in the tenth grade. Unlike during her pregnancy with Esteban, this time she had a test to check the fetal chromosomes—which revealed a normal chromosome 10 with a bit of another chromosome stuck into it. A geneticist at the medical center where Omyra's doctor practiced requested that the family provide DNA samples. She found that the fetus had inherited the unusual chromosome from the father, Andre, but the chromosome charts from father and fetus differed—Andre's had an unusual arrangement of genetic material but apparently a normal amount of it, whereas the fetus had an extra bit of chromosome 17. Esteban's chromosomes had the same abnormality as his future sister's. The geneticist suspected that his various symptoms—developmental delay, social awkwardness, and learning disabilities—may have stemmed from the extra DNA. His little sister Maribella, too, was slow to develop, but is today a very happy preschooler.



Too much genetic material. A piece of the short arm of Andre's chromosome 10 (designated  $10q^-$ ) has moved to one of his chromosome 17s. He is healthy. However, Esteban and Maribella have each inherited the copy of the chromosome 17 with the extra material (designated  $17q^+$ ) as well as two normal chromosome 10s. The extra chromosome 10 DNA caused their symptoms.

Mutations range from single-base changes; to missing or extra exons, genes, pieces of chromosomes, or entire chromosomes; to entire extra sets of chromosomes. The distinction between a gene level and chromosome level of mutation is subjective in that it depends upon what technology enables us to visualize. A mutation has been considered a chromosomal aberration if it is large enough to see with a light microscope using stains and/or fluorescent probes to highlight missing, extra, or moved genetic material. The mutations described in chapter 12 and in this chapter represent a continuum—they differ in scale and in our ability to detect them.

In general, excess genetic material has milder effects on health than a deficit. Still, most large-scale chromosomal abnormalities disrupt or halt prenatal development. As a result, only a few—0.65 percent—of all newborns have chromosomal abnormalities that produce symptoms. An additional 0.20 percent have chromosomal rearrangements in which chromosome parts have been flipped or swapped, but they do not produce symptoms unless they disrupt genes that are crucial to health.

**Cytogenetics** is the subdiscipline within genetics that links chromosome variations to specific traits, including illnesses. Human genome sequence information is adding to our cytogenetics knowledge by identifying which genes contribute which symptoms to chromosome-related syndromes, and by comparing the gene contents of the chromosomes. For example, for decades geneticists did not understand why the most frequently seen extra autosomes in newborns are chromosomes 13, 18, and 21. The human genome sequence revealed that these chromosomes carry far fewer protein-encoding genes than the other autosomes, compared to their total amount of DNA. Therefore, extra copies of these chromosomes are tolerated well enough for some fetuses with them to survive to be born.

This chapter explores several chromosome-level abnormalities and their effects on health. Many actual cases are used to describe some of them.

## 13.1 Portrait of a Chromosome

A chromosome consists primarily of DNA and proteins, and is duplicated and transmitted—via mitosis or meiosis—to the next cell generation. Chromosomes have long been described and distinguished by size and shape, using stains and dyes to contrast dark **heterochromatin** with the lighter **euchromatin**, (figure 13.1). Heterochromatin consists mostly of highly repetitive DNA sequences, whereas euchromatin has more protein-encoding sequences.

### Required Parts: Telomeres and Centromeres

A chromosome must include structures that enable it to replicate and remain intact—everything else is essentially informational cargo (protein-encoding genes and their controls). The essential parts of a chromosome, are:

- telomeres
- origin of replication sites, where replication forks begin to form
- the centromere

Recall from figure 2.17 that **telomeres** are chromosome tips. In humans, each telomere is many repeats of the sequence TTAGGG. In most cell types, telomeres shorten with each mitotic cell division.

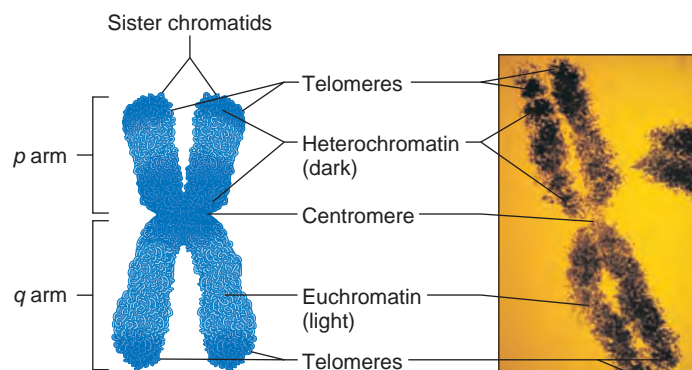
The **centromere** is the largest constriction of a chromosome. It is the place where spindle fibers attach when the cell divides.

A chromosome without a centromere is no longer a chromosome. It vanishes from the cell as soon as division begins because there is no way for it to attach to the spindle.

In humans, many of the hundreds of thousands of DNA bases that form the centromere are repeats of a 171-base DNA sequence called an alpha satellite. (In this usage, *satellite* refers to the fate of these sequences when a chromosome's DNA is shattered and different pieces settle in a density gradient. Because this part of the chromosome settles out at a density separate from the rest of the chromosome, it is called a satellite, just as the moon is a satellite derived from the Earth.) The size and number of repeats in alpha satellites are similar in many species, although the sequence differs. This suggests that satellites have a structural role in maintaining chromosomes rather than an informational role, such as encoding protein.

Centromeres also include centromere-associated proteins. Some of these, synthesized only when mitosis is imminent, form a structure called a kinetochore that contacts the spindle fibers. The kinetochore appears at prophase and apparently vanishes during telophase.

Centromeres are replicated toward the end of S phase. A protein that may control their duplication is called centromere protein A, or CENP-A. Molecules of CENP-A stay with centromeres as chromosomes are replicated, covering about half a million DNA base pairs. When the replicated (sister) chromatids separate at anaphase, each member of the pair retains some CENP-A. The



**Figure 13.1 Portrait of a chromosome.** Tightly wound, highly repetitive heterochromatin forms the centromere (the largest constriction) and the telomeres (the tips) of chromosomes. Elsewhere, lighter-staining euchromatin includes protein-encoding genes. The centromere divides this chromosome into a short arm (*p*) and a long arm (*q*). This chromosome is in the replicated form.



protein therefore passes to the next cell generation, but it is *not* DNA. This is another example of an epigenetic change. The amino acid sequence of CENP-A is nearly identical in diverse species, indicating that it has persisted through evolution and is thus important. CENP-A and other centromere-associated proteins are likely the critical parts of centromeres, rather than the alpha satellite DNA sequences. Evidence for the importance of CENP-A comes from similar DNA sequences that function as “neocentromeres.” They are found throughout the genome in noncentromeric regions, and can function as centromeres if moved, even if they lack alpha satellites.

Centromeres lie within vast stretches of heterochromatin. The arms of the chromosome lie outward from the centromere. Gradually, the DNA includes more protein-encoding sequences as distance from the centromere increases. Gene density varies greatly among chromosomes. Chromosome 21 is a gene “desert,” harboring a million-base stretch with no protein-encoding genes at all. Chromosome 22, in contrast, is a gene “jungle.” These two tiniest chromosomes are remarkably similar in size, but chromosome 22 contains 545 genes to chromosome 21’s 225! **Table 13.1** compares some basic characteristics of five autosomes.

The chromosome parts that lie between protein-rich areas and the telomeres are termed subtelomeres (**figure 13.2**). These areas extend from 8,000 to 300,000 bases inward toward the centromere from the telomeres. Subtelomeres include some protein-encoding genes and therefore bridge the gene-rich regions and the telomere repeats. The transition is gradual. Areas of 50 to 250 bases, right next to the telomeres, consist of 6-base repeats, many of them very similar to the TTAGGG of the telomeres. Then, moving inward from the 6-base zone are many shorter repeats, each present in a few copies. Their function isn’t known. Finally the sequence diversifies and protein-encoding genes appear.

At least 500 protein-encoding genes lie in the total subtelomere regions. About half are members of multigene families (groups of genes of very similar sequence next to each other) that include pseudogenes. These multigene families may reflect recent evolution: Apes and chimps have only one or two genes for many of the large gene families

**Table 13.1**  
**Five Autosomes**

Chromosome	Size in Megabases (millions of bases)	Percentage of Genome	Genes of Interest
5	194.00	6	Acute myelogenous leukemia Basal cell carcinoma Colorectal cancer Dwarfism Salt-resistant hypertension
16	98.00	3	Adult polycystic kidney disease Breast cancer Crohn disease Prostate cancer
19	60.00	2	Atherosclerosis Type 1 diabetes mellitus DNA repair
21	33.55	1	Alzheimer disease Amyotrophic lateral sclerosis Bipolar disorder susceptibility Homocystinuria Usher syndrome
22	33.46	1	Cat eye syndrome Chronic myelogenous leukemia DiGeorge syndrome Schizophrenia susceptibility

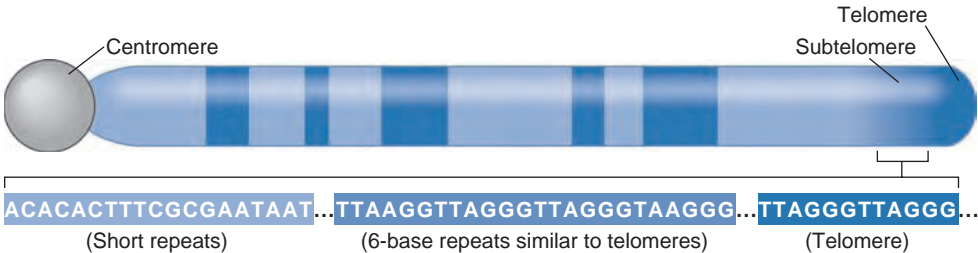
in humans. Such gene organization is one explanation for why our genome sequence is so very similar to that of our primate cousins—but we are clearly different animals. Our genomes differ more in gene copy number and chromosomal organization than in DNA base sequence.

### Karyotypes Chart Chromosomes

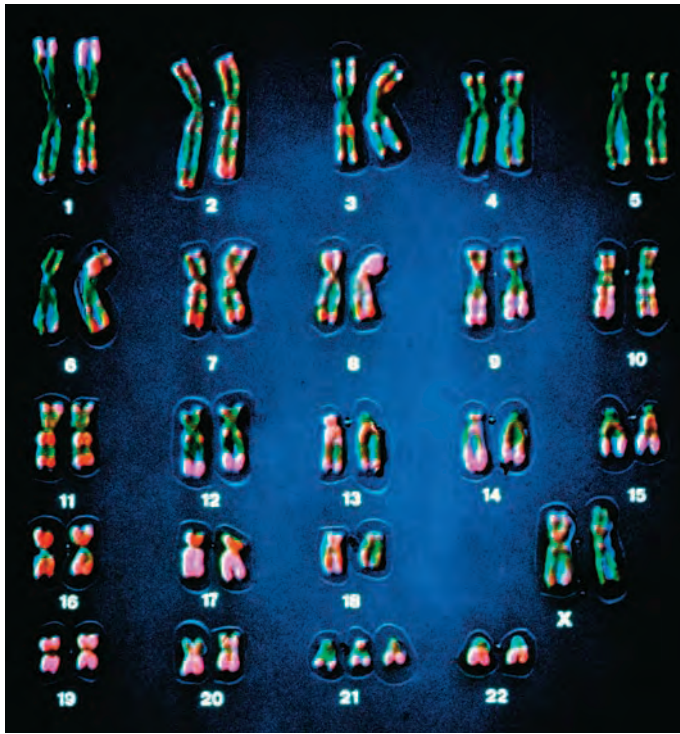
Even in this age of genomics, the standard chromosome chart, or **karyotype**, remains a major clinical tool. A karyotype

displays chromosomes in pairs by size and by physical landmarks that appear during mitotic metaphase, when DNA coils tightly. **Figure 13.3** shows a karyotype with an extra chromosome.

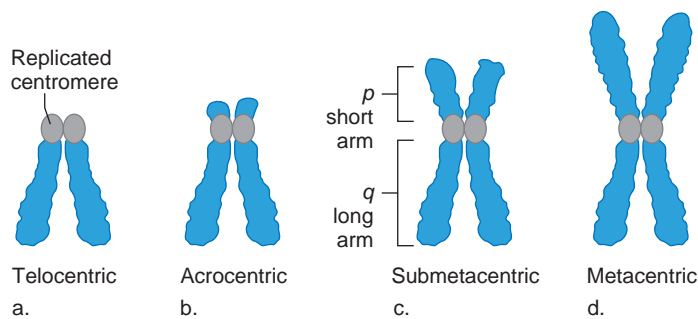
The 24 human chromosome types are numbered from largest to smallest—1 to 22. The other two chromosomes are the X and the Y. Early attempts to size-order chromosomes resulted in generalized groupings because many of the chromosomes are of similar size. Use of dyes and stains made it easier to distinguish chromosomes.



**Figure 13.2 Subtelomeres.** The repetitive sequence of a telomere gradually diversifies toward the centromere. The centromere is depicted as a buttonlike structure to more easily distinguish it, but it is composed of DNA like the rest of the chromosome.



**Figure 13.3** A karyotype displays chromosome pairs in size order. Note the extra chromosome 21 that causes trisomy 21 Down syndrome.



**Figure 13.4** Centromere position distinguishes chromosomes. (a) A telocentric chromosome has the centromere at one end. Humans do not have any telocentric chromosomes. (b) An acrocentric chromosome has the centromere near an end. (c) A submetacentric chromosome's centromere creates a long arm (*q*) and a short arm (*p*). (d) A metacentric chromosome's centromere establishes equal-sized arms.

Centromere position is one physical feature of chromosomes. A chromosome is **metacentric** if the centromere divides it into two arms of approximately equal length. It is **submetacentric** if the centromere establishes one long arm and one short arm, and **acrocentric** if it pinches off only a small amount of material toward one end (figure 13.4). Some species have telocentric chromosomes that have only one arm, but humans do not. The long arm of a chromosome is designated *q*, and the short arm *p* (*p* stands for “petite”).

Five human chromosomes (13, 14, 15, 21, and 22) have bloblike ends, called satellites,

that extend from a thinner, stalklike bridge from the rest of the chromosome. (This use of the word *satellite* differs from the usage of the term in centromeric repeats.) The stalk regions do not bind stains well. The stalks carry many copies of genes encoding ribosomal RNA and ribosomal proteins. These areas coalesce to form the nucleolus, a structure in the nucleus where ribosomal building blocks are produced and assembled (see figure 2.3).

Karyotypes are useful at several levels. When a baby is born with the distinctive facial features of Down syndrome, a karyotype

confirms the clinical diagnosis. Within families, karyotypes are used to identify relatives with a particular chromosomal aberration that can affect health. In one family, several adults died from a rare form of kidney cancer. Karyotypes revealed that the affected individuals all had an exchange, called a **translocation**, between chromosomes 3 and 8. When karyotypes showed that two young family members had the translocation, physicians examined and monitored their kidneys, detecting cancer very early and treating it successfully.

Karyotypes of individuals from different populations can reveal the effects of environmental toxins, if abnormalities appear only in a group exposed to a particular contaminant. Because chemicals and radiation that can cause cancer and birth defects often break chromosomes into fragments or rings, detecting this genetic damage can alert physicians to the possibility that certain cancers may appear in the population.

Karyotypes compared among species can clarify evolutionary relationships. The more recent the divergence of two species from a common ancestor, the more closely related we presume they are, and the more alike their chromosome banding patterns should be. Our closest relative, according to karyotypes, is the pygmy chimpanzee (bonobo). The human karyotype is also remarkably similar to that of the domestic cat, and somewhat less similar to those of mice, pigs, and cows. Among mammals, it is least like the karyotype of the armadillo, indicating that this is a primitive placental mammal.

## Key Concepts

1. A chromosome minimally includes telomeres, origins of replication, and centromeres.
2. A centromere consists of alpha satellite repeats and associated proteins, some of which form the kinetochore, where spindle fibers attach. Centromere protein A enables the centromere to replicate.
3. Subtelomeres contain telomere-like repeats and protein-encoding multigene families.
4. Chromosomes differ by size, centromere location, satellites, and staining. Karyotypes are size-order chromosome charts.

## 13.2 Visualizing Chromosomes

Extra or missing chromosomes are easily detected by counting a number other than 46. Identifying chromosome rearrangements, such as an inverted sequence or an exchange of parts between two chromosomes, requires a way to distinguish among the chromosomes. A combination of stains and DNA probes applied to chromosomes allows this. A **DNA probe** is a labeled piece of DNA that binds to its complementary sequence on a particular chromosome.

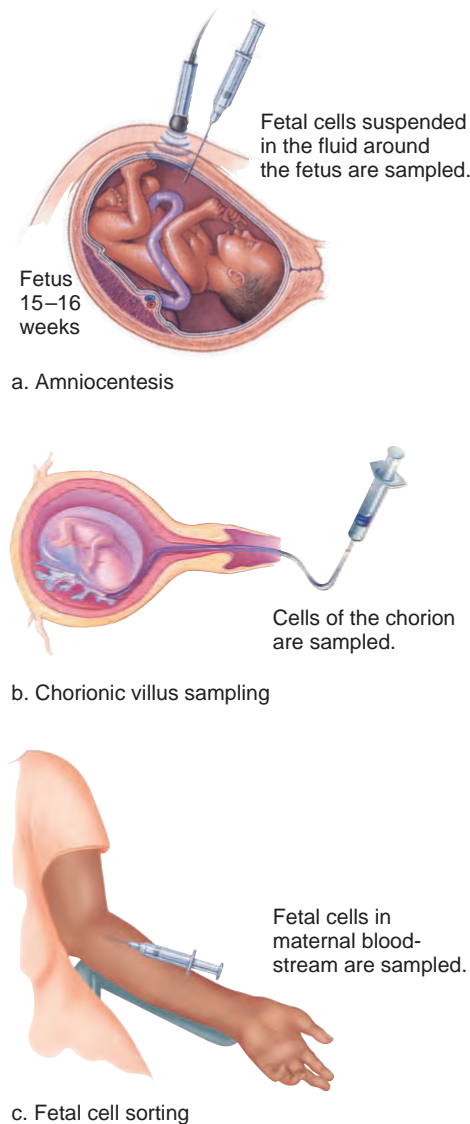
### Obtaining Cells for Chromosome Study

Any cell other than a mature red blood cell (which lacks a nucleus) can be used to examine chromosomes, but some cells are easier to obtain and culture than others. For adults, white blood cells separated from a blood sample or skinlike cells collected from the inside of the cheek are usually used for a chromosome test. A person might require such a test if he or she has a family history of a chromosomal abnormality or seeks medical help because of infertility.

Chromosome tests are commonly performed on cells from fetuses. Couples who receive a prenatal diagnosis of a chromosome abnormality can arrange for treatment of the newborn, if possible; learn more about the condition and contact support groups and plan care; or terminate the pregnancy. These choices are best made after a genetic counselor or physician provides information on the medical condition and treatment options.

### Amniocentesis

The first fetal karyotype was constructed in 1966 using a technique called **amniocentesis**. A doctor removes a small sample of fetal cells and fluids from the uterus with a needle passed through the woman's abdominal wall (**figure 13.5a**). The cells are cultured for a week to 10 days, and typically 20 cells are karyotyped. DNA probes can detect chromosomes in a day or two. The sampled amniotic fluid is also examined for



**Figure 13.5** Three ways to check a fetus's chromosomes.

(a) Amniocentesis draws out amniotic fluid. Fetal cells shed into the fluid are collected and their chromosomes examined. (b) Chorionic villus sampling removes cells that would otherwise develop into the placenta. Since these cells descended from the fertilized ovum, they should have the same chromosomal constitution as the fetus. (c) Improved techniques for extracting and identifying specific cells allow researchers to detect fetal cells in a sample of blood from the woman.

deficient, excess, or abnormal biochemicals that could indicate an inborn error of metabolism. Specific tests are tailored to the patient, based on family history. Ultrasound



**Figure 13.6** A sonogram is an image obtained with ultrasound.

In an ultrasound exam, sound waves bounced off the embryo or fetus are converted into a three-dimensional-appearing image. "4D ultrasound" provides a video of an embryo or fetus. (The fourth dimension is time.)

is used to follow the needle's movement and to visualize fetal parts, such as the profile in **figure 13.6**.

Amniocentesis can detect approximately 1,000 of the more than 5,000 known chromosomal and biochemical problems. Additional tests for single-gene disorders must be requested. The most common chromosomal abnormality detected is one extra chromosome, called a **trisomy**. Amniocentesis is usually performed between 14 and 16 weeks gestation, when the fetus isn't yet very large but amniotic fluid is plentiful. Amniocentesis can be carried out anytime after this point.

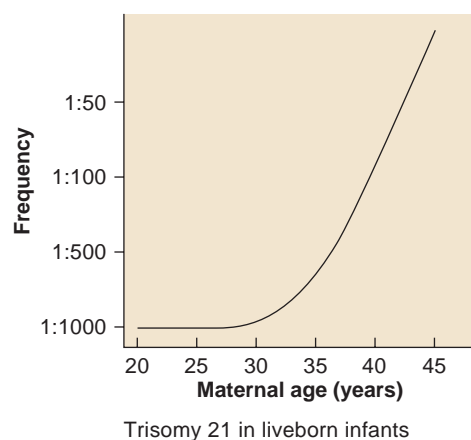
Doctors recommend amniocentesis if the risk that the fetus has a detectable condition exceeds the risk that the procedure will cause a miscarriage (**table 13.2**). Until recently, this risk cutoff was thought to be about age 35 in the woman, when the risk to the fetus of a detectable chromosome problem about equals the risk of amniocentesis causing pregnancy loss—1 in 350. While it is still true that the risk of a chromosomal problem rises steeply after maternal age 35, amniocentesis has become much safer in the 30 or so years since the statistics were obtained that have been used for most risk estimates (**figure 13.7**). In 2007 a large study found the risk of amniocentesis causing



Table 13.2

## Amniocentesis or Chorionic Villus Sampling (CVS)?

Procedure	Gestation Time (weeks)	Cell Source	Route	Added Risk of Miscarriage
CVS	10–12	Chorionic villi	Vagina	8/1,000
Amniocentesis	14–16	Fetal skin, bladder, and digestive system cells in amniotic fluid	Needle in abdomen	1/1,600



**Figure 13.7** The risk of conceiving an offspring with trisomy 21 rises dramatically with maternal age.

miscarriage to be about 1 in 1,600, leading many physicians to lower the age at which they offer amniocentesis. The procedure is also warranted if a couple has had several spontaneous abortions or children with birth defects or a known chromosome abnormality.

Another reason to seek amniocentesis is if a blood test on the pregnant woman reveals low levels of a fetal liver protein called alpha fetoprotein (AFP) and high levels of human chorionic gonadotropin (hCG). These signs may indicate a fetus with a small liver, which may reflect a trisomy. Such “maternal serum marker” tests may assess other biochemicals (estriol, inhibin A, and pregnancy-associated plasma protein A) and consider signs seen on a sonogram that may indicate a chromosome abnormality. For example, increased fluid at the back of the neck (called nuchal translucency) and absent or underdeveloped nasal bones, both characteristic of

Down syndrome, can be seen on sonograms. Maternal serum marker tests have high rates of false negatives and false positives. Because results must be followed up with a more definitive test, such as amniocentesis, maternal serum marker tests are considered screens rather than diagnostic tests.

### Chorionic Villus Sampling

During the 10th through 12th week of pregnancy, **chorionic villus sampling (CVS)** obtains cells from the chorionic villi, the structures that develop into the placenta (figure 13.5b). A karyotype is prepared directly from the collected cells, rather than first culturing them, as in amniocentesis. Results are ready in days.

Because chorionic villus cells descend from the fertilized ovum, their chromosomes should be identical to those of the embryo and fetus. Occasionally, a chromosomal aberration occurs only in a cell of the embryo, or only in a chorionic villus cell. This results in chromosomal mosaicism—the karyotype of a villus cell differs from that of an embryo cell. Chromosomal mosaicism has great clinical consequences. If CVS indicates an abnormality in villus cells that is not also in the fetus, then a couple may elect to terminate the pregnancy when the fetus is actually chromosomally normal. In the opposite situation, the results of the CVS may be normal, but the fetus has abnormal chromosomes.

CVS is slightly less accurate than amniocentesis, and in about 1 in 1,000 to 3,000 procedures, it halts development of the feet and/or hands, a condition termed transverse limb defects. Also, CVS does not sample amniotic fluid, so tests for inborn

errors of metabolism are not possible. The advantage of CVS is earlier results, but the disadvantage is a greater risk of spontaneous abortion.

### Fetal Cell Sorting

Fetal cell sorting, which separates fetal cells from the woman’s bloodstream, is safer than amniocentesis and CVS but is still experimental in the United States (figure 13.5c). The technique traces its roots to 1957, when a pregnant woman died when cells from a very early embryo lodged in a major blood vessel in her lung, blocking blood flow. The fetal cells were detectable because they were from a male, and contained the telltale Y chromosome. This meant that fetal cells could enter a woman’s circulation.

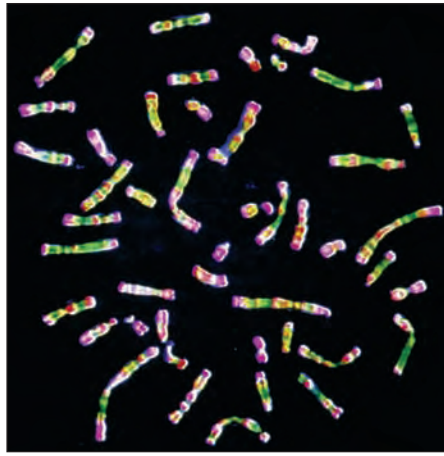
By studying the blood of other pregnant women, researchers found that fetal cells enter the maternal circulation in up to 70 percent of pregnancies. Cells from female embryos, however, cannot easily be distinguished from the cells of the pregnant woman on the basis of sex chromosome analysis. But fetal cells from either sex can be distinguished from maternal cells using a device called a fluorescence-activated cell sorter. It separates fetal cells from maternal blood by identifying surface characteristics that differ from those on the woman’s cells. The fetal cells are then karyotyped and specific gene tests performed on fetal DNA. Free fetal DNA can also be isolated from maternal blood.

### Preparing Cells for Chromosome Observation

Cytogeneticists have tried to describe and display human chromosomes since the late nineteenth century (**figure 13.8**). Then, the prevailing view held that humans had an XO sex determination system, with females having an extra chromosome (XX). Estimates of the human chromosome number ranged from 30 to 80. In 1923, Theophilus Painter published sketches of human chromosomes from three patients at a Texas state mental hospital. The patients had been castrated in an attempt to control their abusive behavior, and Painter was able to examine the removed tissue. He could not at first tell whether the



a.



b.

**Figure 13.8 Viewing chromosomes, then and now.** (a) The earliest drawings of chromosomes, by German biologist Walter Flemming, date from 1882. His depiction captures the random distribution of chromosomes as they splash down on a slide. (b) A micrograph of actual stained human chromosomes.

cells had 46 or 48 chromosomes, but finally decided that he saw 48. Painter later showed that both sexes have the same chromosome number.

The difficulty in distinguishing between 46 or 48 chromosomes was physical—it is challenging to prepare a cell in which chromosomes do not overlap. To easily count the chromosomes, scientists had to find a way to capture them when they are most condensed—during cell division—and also spread them apart. Since the 1950s, cytogeneticists have used colchicine, an extract of the chrysanthemum plant, to arrest cells during division.

### Swelling, Squashing, and Untangling

How to untangle the spaghettilike mass of chromosomes was solved by accident in 1951. A technician mistakenly washed white blood cells being prepared for chromosome analysis in a salt solution that was less concentrated than the interiors of the cells. Water rushed into the cells, swelling them and separating the chromosomes.

In 1955, cell biologists Albert Levan and Joe-Hin Tjio found that when they drew cell-rich fluid into a pipette and dropped it onto a microscope slide prepared with stain, the cells burst open and freed the mass of chromosomes. Adding a glass coverslip spread the chromosomes enough that they could be counted. After many studies of chro-

somes from cultured cells, researchers finally agreed that the number of chromosomes in a diploid human cell is 46, and that the number in gametes is 23.

Karyotypes were once constructed using a microscope to locate a cell where the chromosomes were not touching, photographing the cell, developing a print, cutting out the individual chromosomes, and arranging them into a size-ordered chart. Today, a computer scans ruptured cells in a drop of stain and selects one in which the chromosomes are the most visible and well-spread. Then image analysis software recognizes the band patterns of each stained chromosome pair, sorts the structures into a size-ordered chart, and prints the karyotype. If the software recognizes an abnormal band pattern, a database pulls out identical or similar karyotypes from records of other patients.

### Staining

In the earliest karyotypes, dyes were used to stain chromosomes a uniform color. Chromosomes were grouped into size classes, designated A through G, in decreasing size order. In 1959, scientists described the first chromosomal abnormalities—Down syndrome (an extra chromosome 21), Turner syndrome (also called XO syndrome, a female with only one X chromosome), and Klinefelter syndrome (also called XXY syndrome, a male with an extra X chromosome). Visualizing and distinguishing the sex

chromosomes revealed the causes of these conditions, discussed later in the chapter.

The first chromosome stains could highlight large deletions and duplications, but usually researchers only vaguely understood the nature of a chromosomal syndrome. In 1967, a mentally retarded child with material missing from chromosome 4 would have been diagnosed as having a “B-group chromosome” disorder. Today, geneticists can identify the exact genes that are missing.

Describing smaller chromosomal aberrations required better ways to distinguish chromosomes. In the 1970s, Swedish scientists developed stains that create banding patterns unique to each chromosome. These stains are specific for AT-rich or GC-rich stretches of DNA, or for heterochromatin, which is dark-staining.

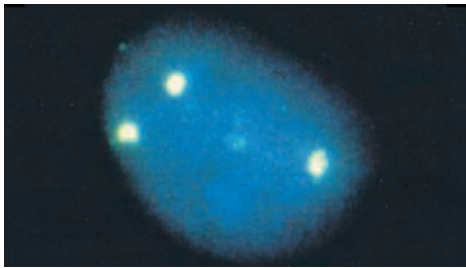
The ability to detect missing, extra, inverted, or misplaced bands allowed researchers to link many more syndromes with specific chromosome aberrations. Then researchers found that synchronizing the cell cycle of cultured cells revealed even more bands per chromosome. Yet another technique, **fluorescence *in situ* hybridization** (FISH), introduced the ability to highlight individual genes.

### FISHing

FISH is more precise and targeted than conventional chromosome staining. FISH uses DNA probes that are complementary to specific DNA sequences. The probes are attached to molecules that fluoresce when illuminated, producing a flash of color precisely where the probe binds to a chromosome in a patient’s sample.

FISH is based on a technique, developed in 1970, called *in situ* hybridization, which originally used radioactive rather than fluorescent labels. *In situ* hybridization took weeks to work, because it relied on exposing photographic film to reveal bound DNA probes. The danger of working with radioactivity, and the crudeness of the results, prompted researchers to seek alternative ways to detect DNA probes.

FISH can “paint” entire karyotypes. Each chromosome is probed with several different fluorescent molecules. A computer integrates the images and creates a unique false color for each chromosome. Many laboratories that perform



**Figure 13.9 FISHing for genes and chromosomes.** FISH shows three fluorescent dots that correspond to three copies of chromosome 21.

amniocentesis or CVS use FISH probes for chromosomes 13, 18, 21, and the X and Y to quickly identify the most common problems. In **figure 13.9**, FISH reveals the extra chromosome 21 in cells from a fetus with trisomy 21 Down syndrome.

A new type of prenatal chromosome analysis amplifies certain repeated sequences on chromosomes 13, 18, 21, X, and Y. The technique distinguishes paternally derived from maternally derived repeats on each homolog for these five chromosomes. An abnormal ratio of maternal to paternal repeats indicates a numerical problem, such as two copies of one parent’s chromosome 21. Combined with the one chromosome 21 from the other parent, this situation would produce a fertilized ovum with three copies of chromosome 21, which causes Down syndrome.

### Chromosomal Shorthand

Geneticists abbreviate the pertinent information in a karyotype by listing chromosome number, then sex chromosome constitution, then abnormal autosomes. Symbols describe the type of aberration, such as a deletion or translocation; numbers correspond to specific bands. A normal male is 46,XY; a normal female is 46,XX. Geneticists use this notation to describe gene locations. For example, the  $\beta$ -globin subunit of hemoglobin is located at 11p15.5. **Table 13.3** gives some examples of chromosomal shorthand.

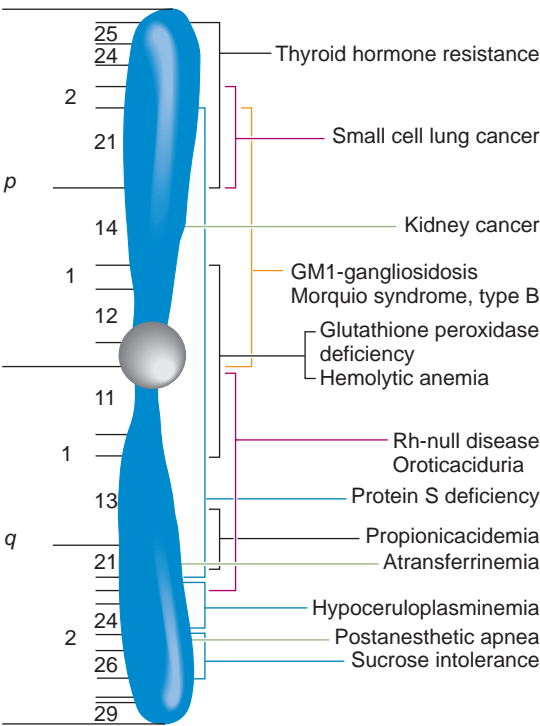
Chromosome information is displayed in an ideogram, which is a graphical representation of a karyotype (**figure 13.10**).

The chromosome is divided into numbered regions and subregions. Specific gene loci are listed on the right side. Ideograms are

becoming so crowded with notations indicating specific genes that they may soon become obsolete.

**Table 13.3**  
Chromosomal Shorthand

Abbreviation	What It Means
46,XY	Normal male
46,XX	Normal female
45,X	Turner syndrome (female)
47,XXY	Klinefelter syndrome (male)
47,XYY	Jacobs syndrome (male)
46,XY, del (7q)	A male missing part of the long arm of chromosome 7
47,XX, +21	A female with trisomy 21 Down syndrome
46,XY, t(7;9)(p21.1; q34.1)	A male with a translocation between the short arm of chromosome 7 at band 21.1 and the long arm of chromosome 9 at band 34.1
48, XXYY	A male with an extra X and an extra Y



**Figure 13.10 Ideogram.** An ideogram is a schematic chromosome map. It indicates chromosome arm (p or q), major regions delineated by banding patterns, and the loci of selected genes. This is a partial map of human chromosome 3.



## Key Concepts

1. Karyotypes display chromosomes in size order.
2. Chromosomes can be visualized in any cell that has a nucleus and can be cultured.
3. Fetal karyotypes are made from cells obtained by amniocentesis, CVS, or fetal cell sorting from maternal blood. Maternal serum marker patterns and ultrasound scans can reveal increased risk of an abnormal chromosome number.
4. Cytogeneticists obtain cells; display, stain, and probe chromosomes with fluorescent molecules; and then arrange them in a karyotype.
5. Chromosomal shorthand summarizes the number of chromosomes, sex chromosome constitution, and type of aberration. Ideograms display features of individual chromosomes.

### 13.3 Abnormal Chromosome Number

A human karyotype is abnormal if the number of chromosomes in a somatic cell is not 46, or if individual chromosomes have extra, missing, or rearranged genetic material. **Table 13.4** summarizes the types of chromosome abnormalities in the order in which they are discussed.

Abnormal chromosomes account for at least 50 percent of spontaneous abortions, yet only 0.65 percent of newborns have abnormal chromosomes. Those that survive to be born usually have “balanced chromosome rearrangements,” which means that all of the genetic material is present, but part is inverted in DNA sequence or found on a chromosome that does not ordinarily include that sequence. Therefore, most embryos and fetuses with abnormal chromosomes stop developing before birth.

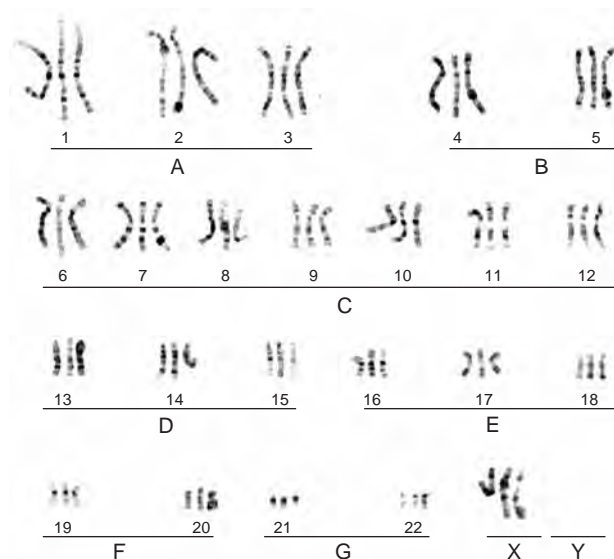
#### Polyploidy

The most drastic upset in chromosome number is an entire extra set. A cell with extra sets of chromosomes is **polyploid**. An individual whose cells have three copies of each chromosome is a triploid (designated

**Table 13.4**

#### Chromosome Abnormalities

Type of Abnormality	Definition
Polyploidy	Extra chromosome sets
Aneuploidy	An extra or missing chromosome
Monosomy	One chromosome absent
Trisomy	One chromosome extra
Deletion	Part of a chromosome missing
Duplication	Part of a chromosome present twice
Translocation	Two chromosomes join long arms or exchange parts
Inversion	Segment of chromosome reversed
Isochromosome	A chromosome with identical arms
Ring chromosome	A chromosome that forms a ring due to deletions in telomeres, which cause ends to adhere



**Figure 13.11 Polyploids in humans are lethal.** Individuals with three copies of each chromosome (triploids) in every cell account for 17 percent of all spontaneous abortions and 3 percent of stillbirths and newborn deaths.

3N, for three sets of chromosomes). Two-thirds of all triploids result from fertilization of an oocyte by two sperm. The other cases arise from formation of a diploid gamete, such as when a normal haploid sperm fertilizes a diploid oocyte. Triploids account for 17 percent of spontaneous abortions (**figure 13.11**). Very rarely, an infant survives as long as a few days, with defects in nearly all organs.

Polyploids are very common among flowering plants, including roses, cotton, barley, and wheat, and in some insects.

Certain human cells may be polyploid. The liver, for example, has some tetraploid (4N) and even octaploid (8N) cells.

#### Aneuploidy

Cells missing a single chromosome or having an extra one are **aneuploid**, which means “not good set.” Rarely, aneuploids can have more than one missing or extra chromosome, indicating defective meiosis in a parent. A normal chromosome number is **euploid**, which means “good set.”

Most autosomal aneuploids (with a missing or extra non-sex chromosome) are spontaneously aborted. Those that survive have specific syndromes, with symptoms depending upon which chromosomes are missing or extra. Mental retardation is common in aneuploidy because development of the brain is so complex and of such long duration that nearly any chromosome-scale disruption affects genes whose protein products affect the brain. Sex chromosome aneuploidy usually produces milder symptoms.

Most children born with the wrong number of chromosomes have an extra chromosome (a trisomy) rather than a missing one (a monosomy). Most monosomies are so severe that an affected embryo ceases developing. Trisomies and monosomies are named for the chromosomes involved, and in the past the associated syndromes were named for the discoverers. Today, cytogenetic terminology is used because it is more precise. For example, Down syndrome can result from a trisomy or a translocation. The distinction is important in genetic counseling. Translocation Down syndrome, although accounting for only 4 percent of cases, has a much higher recurrence risk within a family than the trisomy form, a point we return to later in the chapter.

The meiotic error that causes aneuploidy is called **nondisjunction**. Recall that in normal meiosis, homologs separate and each of the resulting gametes receives only one member of each chromosome pair. In nondisjunction, a chromosome pair fails to separate at anaphase of either the first or second meiotic division. This produces a sperm or oocyte that has two copies of a particular chromosome, or none, rather than the normal one copy (**figure 13.12**). When such a gamete fuses with its partner at fertilization, the zygote has either 45 or 47 chromosomes, instead of the normal 46. Different trisomies tend to be caused by nondisjunction in the male or female, at meiosis I or II.

A cell can have a missing or extra chromosome in 49 ways—an extra or missing copy of each of the 22 autosomes, plus the five abnormal types of sex chromosome combinations—Y, X, XXX, XXY, and XYY. (Sometimes individuals have four or even

five sex chromosomes.) However, only nine types of aneuploids are recognized in newborns. Others are seen in spontaneous abortions or fertilized ova intended for *in vitro* fertilization.

Most of the 50 percent of spontaneous abortions that result from extra or missing chromosomes are 45,X individuals (missing an X chromosome), triploids, or trisomy 16. About 9 percent of spontaneous abortions are trisomy 13, 18, or 21. More than 95 percent of newborns with abnormal chromosome numbers have an extra 13, 18, or 21, or an extra or missing X or Y chromosome. These conditions are all rare at birth—together they affect only 0.1 percent of all children. But nondisjunction occurs in 5 percent of recognized pregnancies.

Types of chromosome abnormalities seem to differ between the sexes. Abnormal oocytes mostly have extra or missing chromosomes, whereas abnormal sperm more often have structural variants, such as inversions or translocations, discussed later in the chapter.

Aneuploidy and polyploidy also arise during mitosis, producing groups of somatic cells with the extra or missing chromosome. An individual with two chromosomally distinct cell populations is a mosaic. If only a few cells are altered, health may not be affected. However, a mitotic abnormality that occurs early in development, so that many cells descend from the unusual one, can affect health. A chromosomal mosaic for a trisomy may have a mild version of the associated condition. This is usually the case for the 1 to 2 percent of people with Down syndrome who are mosaic. The phenotype depends upon which cells have the extra chromosome. Unfortunately, prenatal testing cannot reveal which cells are affected.

## Autosomal Aneuploids

Most autosomal aneuploids cease developing long before birth. Following are cases and descriptions of the most common autosomal aneuploids among liveborns. The information is summarized in **Table 13.5**.

### Trisomy 21—David's Story

*When David G. was born in 1994, doctors told his 19-year-old mother, Toni, to put him*

*into an institution. "They said he wouldn't walk, talk, or do anything. Today, I want to bring him back and say look, he walks and talks and runs track and is graduating high school," says Toni.*

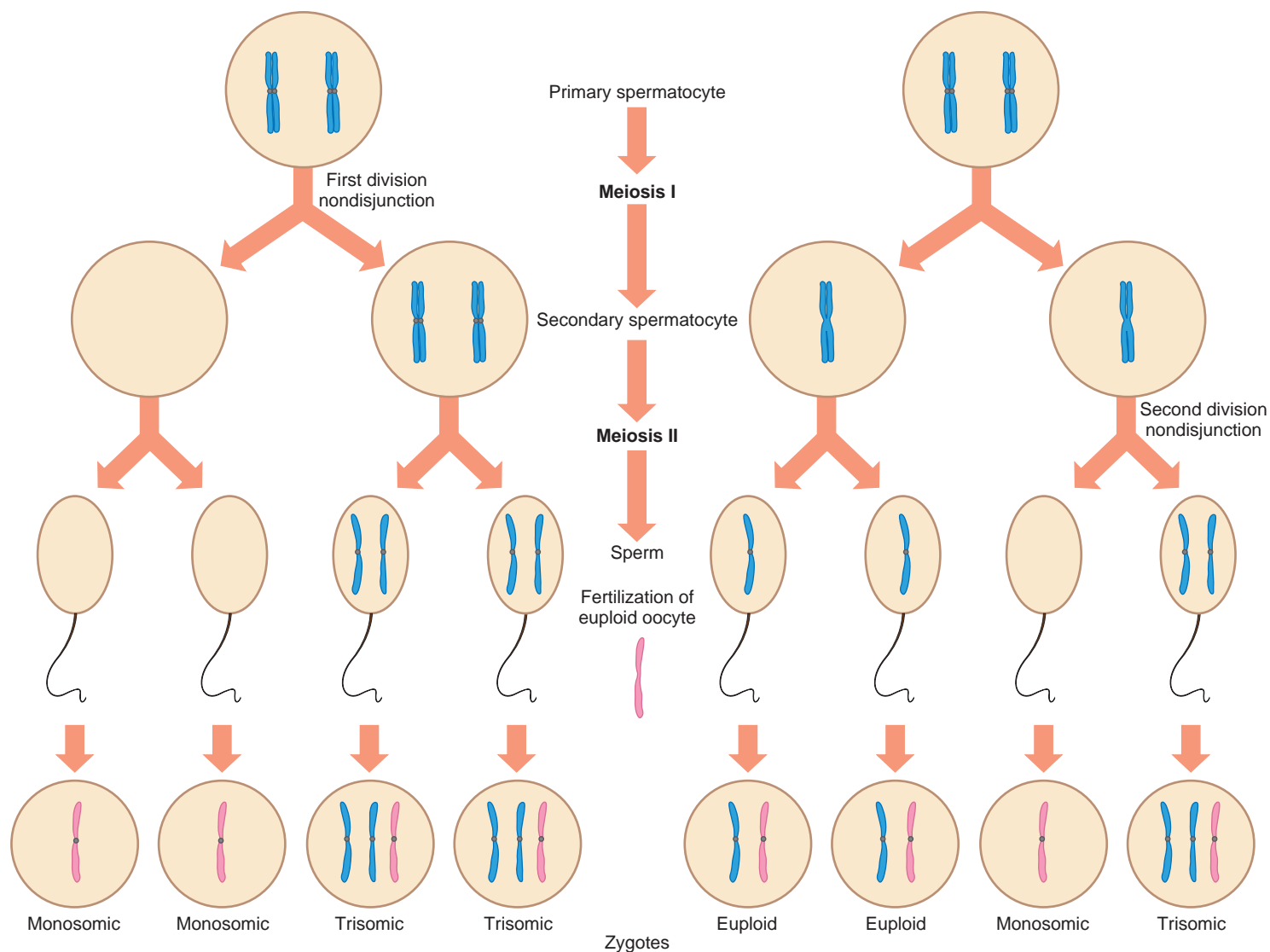
*Like other teens, David has held part-time jobs, gone to dances, and uses a computer. But he is unlike most other teens in that his cells have an extra chromosome 21, which limits his intellectual abilities. "Maybe he's not book smart, but when you look around at what he can do, he's smart," Toni says. His speech is difficult to understand, and he has facial features characteristic of Down syndrome, but he has a winning personality and close friends. Still, Toni fears that he will meet few people like himself as he gets older, because studies report that 90 percent of couples told their fetus has Down syndrome choose to end the pregnancy.*

*Sometimes David gets into unusual situations because he takes things literally. He once dialed 911 when he stubbed his toe, because he'd been told to do just that when he was hurt. Overall he's done so well that he plans to move into a group home and find a job after high school.*

The most common autosomal aneuploid among liveborns is trisomy 21. The extra folds in the eyelids, called epicanthal folds, and flat face prompted Sir John Langdon Haydon Down to term the condition *mongoloid* when he described it in 1866. As the medical superintendent of a facility for the profoundly mentally retarded, Down noted that about 10 percent of his patients resembled people of Mongolian heritage. The resemblance is superficial. People of all ethnic groups are affected.

Researchers suspected a link between Down syndrome and an abnormal chromosome number as long ago as 1932. In 1958, 47 chromosomes were identified in cells of a person with Down syndrome, and by 1959, researchers had implicated chromosome 21. In 1960, they discovered Down syndrome caused by a translocation between chromosome 21 and another chromosome, and in 1961, researchers identified mosaic Down syndrome. The girl with mosaicism had physical signs of Down syndrome, but normal intelligence.

A person with Down syndrome is usually short and has straight, sparse hair and a tongue protruding through thick lips. The



a. Nondisjunction at meiosis I

b. Nondisjunction at meiosis II

**Figure 13.12 Extra and missing chromosomes—aneuploidy.** Unequal division of chromosome pairs can occur at either the first or second meiotic division. **(a)** A single pair of chromosomes is unevenly partitioned into the two cells arising from meiosis I in a male. The result: two sperm cells have two copies of the chromosome, and two sperm cells have no copies. When a sperm cell with two copies of the chromosome fertilizes a normal oocyte, the zygote is trisomic; when a sperm cell lacking the chromosome fertilizes a normal oocyte, the zygote is monosomic. **(b)** This nondisjunction occurs at meiosis II. Because the two products of the first division are unaffected, two of the mature sperm are normal and two are aneuploid. Oocytes can undergo nondisjunction as well, leading to zygotes with extra or missing chromosomes when normal sperm cells fertilize them.

**Table 13.5**

### Comparing and Contrasting Trisomies 13, 18, and 21

Type of Trisomy	Incidence at Birth	Percent of Conceptions That Survive 1 Year After Birth
13 (Patau)	1/12,500–1/21,700	<5%
18 (Edward)	1/6,000–1/10,000	<5%
21 (Down)	1/800–1/826	85%

hands have an abnormal pattern of creases, the joints are loose, and poor reflexes and muscle tone give a “floppy” appearance. Developmental milestones (such as sitting, standing, and walking) come slowly, and toilet training may take several years. Intelligence varies greatly. Parents of a child with Down syndrome can help their child reach maximal potential by providing a stimulating environment. Some people



with Down syndrome can attend college and hold jobs (**figure 13.13**).

Many people with Down syndrome have physical problems, including heart and kidney defects and hearing and vision loss. A suppressed immune system can make

influenza deadly. Digestive system blockages are common and may require surgical correction. A child with Down syndrome is 15 times more likely to develop leukemia than a child who does not have the syndrome, but this is still only a 1 percent risk.

Many of the medical problems associated with Down syndrome are treatable, so that more than 70 percent of affected individuals live beyond age 30, and many live much longer. In 1910, life expectancy was only nine years.

Some people with Down syndrome who pass age 40 develop the black fibers and tangles of amyloid beta protein in their brains characteristic of Alzheimer disease, although they usually do not become severely demented. The chance of a person with trisomy 21 developing Alzheimer disease is 25 percent, compared to 6 percent for the general population. A gene on chromosome 21 causes one inherited form of Alzheimer disease. Perhaps the extra copy of the gene in trisomy 21 has a similar effect to a mutation in the gene that causes Alzheimer disease, such as causing amyloid beta buildup.

Before the human genome sequence became available, researchers studied people who have a third copy of only part of chromosome 21 to identify specific genes that could cause symptoms. **Table 13.6** lists some genes known to contribute to trisomy 21 Down syndrome symptoms.

The likelihood of giving birth to a child with Down syndrome increases dramatically with the age of the mother (see figure 13.7). However, 80 percent of children with trisomy 21 are born to women under age 35, because younger women are more likely to become pregnant and less likely to have amniocentesis. About 90 percent of trisomy 21 conceptions are due to nondisjunction during meiosis I in the female. The 10 percent of cases due to the male result from nondisjunction during meiosis I or II. The chance that trisomy 21 will recur in a family, based on empirical data (how often it actually does recur in families), is 1 percent.

The age factor in trisomy 21 Down syndrome and other trisomies may reflect the fact that the older a woman is, the longer her oocytes have been arrested on the brink of completing meiosis. This is a time period of 15 to 45 years. During their long existence in the ovary, oocytes may have been exposed to toxins, viruses, and radiation. A second possible explanation for the maternal age effect is that females have a pool of immature aneuploid oocytes resulting from nondisjunction. As a woman ages, selectively



**Figure 13.13** Many people who have Down syndrome go to school or have jobs. This young woman is learning how to be a pastry chef.

**Table 13.6****Genes Associated with Trisomy 21 Down Syndrome**

Gene Product	OMIM	Signs and Symptoms (Phenotype)
Amyloid precursor protein (APP)	104760	Protein deposits in brain
Chromatin assembly factor I (CAF1A)	601245	Impaired DNA synthesis
Collagen type VI (COL6A1)	120220	Heart defects
Crystallin (CRYA1)	123580	Cataracts
Cystathione beta synthase (CBS)	236200	Impaired metabolism and DNA repair
Interferon receptor 1 (IFNAR)	107450	Impaired immunity
Kinase 1 (DYRK1A)	600855	Mental retardation
Oncoprotein ETS2 (ETS2)	164740	Skeletal abnormalities, cancer
Phosphoribosylglycinamide formyltransferase (GART)	138440	Impaired DNA synthesis and repair
Superoxide dismutase (SOD1)	147450	Premature aging

releasing normal oocytes each month, the abnormal ones remain, much as black jelly-beans accumulate as people preferentially eat the colored ones. Yet a third possible explanation for the maternal age effect is that trisomies result from gametes in which a homolog pair do not extensively cross over during meiosis I. Such chromosomes tend to migrate to the same pole, packaging an extra chromosome into a gamete.

The association between maternal age and Down syndrome has been recognized since the nineteenth century, when physicians noticed that affected babies were often the youngest children in large families. The syndrome was thought to be caused by syphilis, tuberculosis, thyroid malfunction, alcoholism, or emotional trauma. In 1909, a study of 350 affected infants revealed an overrepresentation of older mothers, prompting some researchers to attribute the link to “maternal reproductive exhaustion.” In 1930, another study found that the increased risk of Down syndrome correlated to maternal age, and not to the number of children in the family.

**Trisomy 18—Anthony’s Story**

*When an ultrasound scan early in pregnancy revealed a small fetus with low-set ears, a small jaw, a pocket of fluid in the brain, and a peculiarly clenched fist, the parents-to-be, Elisa and Brendan,*

*were advised to have amniocentesis to view the fetus’s chromosomes—the signs on the scan suggested an extra chromosome 18. Amniocentesis confirmed what the ultrasound suggested. Although Elisa and Brendan were stunned and upset to learn what lay ahead, they chose to continue the pregnancy. The fetus remained small, as Elisa swelled hugely with three times the normal volume of amniotic fluid. Further ultrasound scans revealed that only one of the kidneys worked, the heart had holes between the chambers, and part of the intestine lay outside the stomach in a sac, so tube feeding would be necessary. The child*

*would be severely developmentally delayed and mentally retarded. Anthony was delivered at 36 weeks after his heart rate became erratic during a routine prenatal visit. He lived only 22 days.*

Trisomies 18 and 13 were described in the same research report in 1960 (**figure 13.14**). Trisomy 18 is also called Edward syndrome and trisomy 13 is also known as Patau syndrome. Most affected individuals do not survive to be born.

Children who have trisomy 18 have great physical and mental disabilities, with developmental skills usually stalled at the six-month level. Major abnormalities include heart defects, a displaced liver, growth retardation, and oddly clenched fists. Milder signs include overlapping placement of fingers, a narrow and flat skull, abnormally shaped and low-set ears, a small mouth and face, unusual or absent fingerprints, short, large toes with fused second and third toes, and “rocker-bottom” feet. Most cases of trisomy 18 are traced to nondisjunction in meiosis II of the oocyte.

**Trisomy 13—Tykesia’s Story**

*At 15 months of age, Tykesia is a “long-term survivor” of trisomy 13. About 92 percent of infants born with an extra chromosome 13 do not live to see their first birthdays.*

*Tykesia is small for her age, at the 5th percentile for weight, but she is happy, curious and playful. Her physical skills, however, lag. She can finally, with great effort, sit up, but*

**Figure 13.14** Trisomies 18 and 13.

(a) An infant with trisomy 18 clenches the fists in an odd way, with fingers overlapping. (b) Very few babies with trisomy 13 are as healthy as Hazel. Most die in infancy.



cannot yet crawl. She has about 20 minor seizures a day, which look like jerks or startles, and has difficulty eating because of persistent acid reflux. She is also missing a rib. Early surgeries corrected a cleft lip and palate, removed an extra finger and toe, and corrected a hernia. Blood vessels leading from the heart to the lungs that did not close as they normally should before birth did so by the time Tykesia was six months old. She is mentally retarded, but her parents hope she will live long enough to attend preschool. Despite these challenges, Tykesia's case is mild—she has her sight and hearing, unlike many others with trisomy 13.

Trisomy 13 has a different set of signs and symptoms than trisomy 18. Most striking is a fusion of the developing eyes, so that a fetus has one large eyelike structure in the center of the face. More common is a small or absent eye. Major abnormalities affect the heart, kidneys, brain, face, and limbs. The nose is often malformed, and cleft lip and/or palate is present in a small head. There may be extra fingers and toes. Ultrasound examination of an affected newborn often reveals more extensive anomalies than were visualized prenatally, such as an extra spleen, abnormal liver, rotated intestines, and an abnormal pancreas. A few individuals have survived until adulthood, but they do not progress developmentally beyond the six-month level.

Sex Chromosome Aneuploids: Female

People with sex chromosome aneuploidy have extra or missing sex chromosomes. Table 13.7 indicates how these aneuploids can arise. Note that some conditions can result from nondisjunction in meiosis in the male or female.

XO Syndrome—Miranda's Story

Miranda was well into her teen years, but still looked about 12. It wasn't just that she was short. Her breasts had never developed, and she still hadn't gotten her first menstrual period. Her sister Charlotte, two years younger, actually looked older. When Miranda turned 16, her physician suggested that she have her chromosomes checked. While reassuring Miranda that delayed puberty could be treated, the doctor also explained what she was looking to rule out—absence of an X chromosome, called Turner or XO syndrome.

Table 13.7

How Nondisjunction Leads to Sex Chromosome Aneuploids

Situation	Oocyte	Sperm	Consequence
Normal	X	Y	46,XY normal male
	X	X	46,XX normal female
Female nondisjunction	XX	Y	47,XXY Klinefelter syndrome
	XX	X	47,XXX triplo-X
		Y	45,Y nonviable
		X	45,X Turner syndrome
Male nondisjunction (meiosis I)	X		45,X Turner syndrome
	X	XY	47,XXY Klinefelter syndrome
Male nondisjunction (meiosis II)	X	XX	47,XXX triplo-X
	X	YY	47,XYY Jacobs syndrome
	X		45,X Turner syndrome
Male and female non-disjunction	XX	YY	48,XXYY syndrome

Miranda indeed lacked a second X chromosome. The diagnosis explained other problems she'd had, some obvious, some rather subtle. She'd always had poor hearing and high blood pressure, and the syndrome also accounted for her low thyroid function and the "beauty marks" that dotted her skin. Life with a single X had also affected Miranda's mind, although in mild ways—she had difficulty solving math problems that required envisioning objects in three-dimensional space, and had a poor memory. Miranda started taking estrogen and progesterone, which made her develop secondary sexual characteristics, and her doctor explained that one day she could use a donor egg to become pregnant. Had Miranda known about her unusual chromosomes before her teen years, she could have started taking growth hormones to maximize her height. But Miranda has no regrets—she's smart and happy.

In 1938, at a medical conference, a U.S. endocrinologist named Henry Turner described seven young women, aged 15 to 23, who were sexually undeveloped, short, had folds of skin on the back of their necks, and had malformed elbows. (Eight years earlier, an English physician named Ullrich had described the syndrome in young girls, so it is called Ullrich syndrome in the U.K.) Alerted to what would become known as

Turner syndrome in the United States, other physicians soon began identifying such patients. Physicians assumed that a hormonal insufficiency caused the symptoms. They were right, but there was more to the story—a chromosomal imbalance caused the hormone deficit.

In 1954, at a London hospital, a physician discovered that cells from Turner patients lacked a Barr body, the dark spot that indicates a second X chromosome. Might lack of a sex chromosome cause the symptoms, particularly failure to mature sexually? By 1959, karyotyping confirmed the presence of only one X chromosome. Later, researchers learned that only 50 percent of affected individuals are XO. The rest are missing only part of an X chromosome or are mosaics, with only some cells missing an X.

Like the autosomal aneuploids, Turner syndrome, now called XO syndrome, is found more frequently among spontaneously aborted fetuses than among newborns—99 percent of XO fetuses are not born. The syndrome affects 1 in 2,500 female births. However, if amniocentesis or CVS was not done, a person with XO syndrome would likely not know she has a chromosome abnormality until she lags in sexual development. Two X chromosomes are necessary for normal sexual development in females.



At birth, a girl with XO syndrome looks normal, except for puffy hands and feet caused by impaired lymph flow. In childhood, signs of XO syndrome include wide-set nipples, soft nails that turn up at the tips, slight webbing at the back of the neck, short stature, coarse facial features, and a low hairline at the back of the head. About half of people with XO syndrome have impaired hearing and frequent ear infections due to a small defect in the shape of the coiled part of the inner ear. They cannot hear certain frequencies of sound.

At sexual maturity, sparse body hair develops, but the girls do not ovulate or menstruate, and their breasts do not develop. The uterus is very small, but the vagina and cervix are normal size. In the ovaries, oocytes speed through development, depleting the supply during infancy. Intelligence is normal. However, “Turner neurocognitive phenotype” may impair the ability to solve math problems that entail envisioning objects in three-dimensional space, and may cause memory deficits. Hormones (estrogen and progesterone) can be given to stimulate development of secondary sexual structures for individuals diagnosed before puberty, and prompt use of growth hormone can maximize height. Because of the mild symptoms of sex chromosome aneuploidy compared to autosomal aneuploidy, many individuals are not diagnosed until or after adolescence.

Although women with XO syndrome are infertile, individuals who are mosaics (only some cells lack the second X chromosome) may have children, but they are at high risk of conceiving offspring that have abnormal numbers of chromosomes. XO syndrome is unrelated to the age of the mother. The effects of XO syndrome continue past the reproductive years. Life span is shortened slightly. Adults are more likely to develop certain disorders than the general population, including osteoporosis, types 1 and 2 diabetes, and colon cancer.

The many signs and symptoms of XO syndrome result from the loss of specific genes. For example, loss of a gonadal dysgenesis gene accounts for the ovarian failure, whereas absence of a homeobox gene, which is a transcription factor, causes short stature. Deletion of another gene causes the unusual hearing defect.

### Triplo-X

About 1 in every 1,000 females has an extra X chromosome in each of her cells, a condition called triplo-X. The only symptoms are tall stature and menstrual irregularities. Although triplo-X females are rarely mentally retarded, they tend to be less intelligent than their siblings. The lack of symptoms reflects the protective effect of X inactivation—all but one of the X chromosomes is inactivated. One young woman who has four X chromosomes has learning disabilities that impair her use and understanding of language, a high palate (roof of the mouth), and lax joints.

### Sex Chromosome Aneuploids: Male

Any individual with a Y chromosome is a male.

#### XXY Syndrome—Stefan’s Story

*Looking back, Stefan Schwarz’s only indication of XXY syndrome was small testes. When his extra X chromosome was detected when he was 25, suddenly his personality quirks made sense.*

*“I was very shy, reserved, and had trouble making friends. I would fly into rages for no apparent reason. My parents knew when I was very young that there was something about me that wasn’t right,” he recalls.*

*Many psychologists, psychiatrists, and therapists diagnosed “learning disabilities,” and one even told Stefan he “was stupid and lazy, and would never amount to anything.” But Stefan proved them wrong. He earned two bachelor’s degrees, then started a successful career as a software engineer. Today he heads a support group for men with XXY syndrome.*

About 1 in 1,000 males has the extra X chromosome that causes XXY (Klinefelter) syndrome. Severely affected men are underdeveloped sexually, with rudimentary testes and prostate glands and sparse pubic and facial hair. They have very long arms and legs, large hands and feet, and may develop breast tissue. XXY syndrome is the most common genetic or chromosomal cause of male infertility.

Testosterone injections during adolescence can limit limb lengthening and prompt development of secondary sexual characteristics. Boys and men with XXY syndrome may be slow to learn, but they are

usually not mentally retarded unless they have more than two X chromosomes, which is rare. Many men with XXY syndrome discover it only when they have a fertility problem and their chromosomes are checked. Some affected men probably never learn that they have XXY syndrome.

Men with XXY syndrome have fathered children, with medical assistance. Doctors select sperm that contain only one sex chromosome and use the sperm to fertilize oocytes. However, sperm from men with XXY syndrome are more likely to have extra chromosomes—usually X or Y, but also autosomes—than sperm from men who do not have XXY syndrome.

#### XXYY Syndrome—Devon’s Story

*Devon’s parents suspected early on that he was different. His problems were so common, however, that it was years before a chromosome check revealed an extra X and an extra Y.*

*As a toddler, Devon sat, crawled, and walked more slowly than normal. He was also late to talk, and when he did, his speech was not easily understood. In preschool, problems emerged. He’d have frequent outbursts that seemed to come out of nowhere, and would make inappropriate comments, such as telling a classmate her dress was ugly. He was tall and clumsy, and drooled and choked easily. Devon would run about flapping his arms, then hide under a chair. Severe ulcers formed on his legs. These problems made it difficult for him to make friends.*

*By the second grade, Devon’s difficulties alarmed his special education teacher, who suggested to Devon’s parents, Drucilla and Neil, that they have his chromosomes checked. They did. Since Drucilla and Neil’s chromosomes were normal, Devon must have been conceived from a very unusual oocyte meeting a very unusual sperm, both arising from nondisjunction. The extra sex chromosomes explained nearly all of the boy’s problems, and even a few that hadn’t been recognized, such as curved pinkies, flat feet, and scoliosis. He began receiving testosterone injections so that his teen years would be more normal than his difficult childhood had been.*

A male with an extra X chromosome and an extra Y chromosome was until recently classified as having Klinefelter syndrome. Increased use of amniocentesis to check

fetal chromosomes, however, has made it possible to distinguish XYY from XXY individuals. Even though they share many characteristics, those with the second Y have more severe behavioral problems and tend to develop leg ulcers (**figure 13.15**). The ulcers are believed to result from poor venous circulation.

In XYY syndrome, childhood and adolescence often include attention deficit disorder, obsessive compulsive disorder, and learning disabilities. In the teen years, testosterone level is low, development of secondary sexual characteristics is delayed, and the testes are undescended. A man with XYY syndrome is infertile.

### XYY Syndrome

*In 1961, a tall, healthy man, known for his boisterous behavior, had a chromosome check after fathering a child with Down syndrome. The man had an extra Y chromosome. A few other cases were detected over the next several years.*

*In 1965, researcher Patricia Jacobs published results of a survey among 197 inmates at Carstairs, a high-security prison in Scotland. Of 12 men with unusual chromosomes, seven had an extra Y. Might their violent or aggressive behavior be linked to their extra Y chromosome? Jacobs's findings were repeated for mental institutions, and soon after, Newsweek magazine ran a cover story on "congenital criminals." Having an extra Y, known as Jacobs syndrome, became a legal defense.*

*In the early 1970s, newborn screens began in hospital nurseries in England, Canada, Denmark, and Boston. Social workers and psychologists visited XYY boys and offered "anticipatory guidance" to the parents on how to deal with their toddling future criminals. By 1974, geneticists and others halted the program, pointing out that singling out these boys on the basis of a few statistical studies was inviting self-fulfilling prophecy.*

One male in 1,000 has an extra Y chromosome. Today, we know that 96 percent of XYY males are apparently normal. The only symptoms attributable to the extra chromosome may be great height, acne, and perhaps speech and reading problems. An explanation for the continued prevalence of XYY among mental-penal institution populations may be more psychological than biological. Large body size may lead teachers, employers, parents, and others to expect more of these people, and a few XYY individuals may deal with this stress aggressively.

Jacobs syndrome can arise from nondisjunction in the male, producing a sperm with two Y chromosomes that fertilizes an X-bearing oocyte. Geneticists have never observed a sex chromosome constitution of one Y and no X. Since the Y chromosome carries little genetic material, and the gene-packed X chromosome would not be present, the absence of so many genes makes development beyond a few cell divisions in a YO embryo impossible.



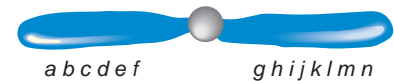
**Figure 13.15 XYY syndrome is rare.** Many affected boys develop foot and leg ulcers, due to poor circulation.

## Key Concepts

1. Polyploids have extra sets of chromosomes and do not survive for long.
2. Aneuploids have extra or missing chromosomes. Nondisjunction during meiosis causes aneuploidy.
3. Trisomies are less severe than monosomies, and sex chromosome aneuploidy is less severe than autosomal aneuploidy.
4. Mitotic nondisjunction produces chromosomal mosaics.
5. Down syndrome (trisomy 21) is the most common autosomal aneuploid, followed by trisomies 18 and 13.
6. Sex chromosome aneuploid conditions include XO, triplo-X, XXY, XYY, and XYY syndromes.

## 13.4 Abnormal Chromosome Structure

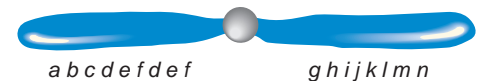
Structural chromosomal defects include missing, extra, or inverted genetic material within a chromosome or combined or exchanged parts of nonhomologs (translocations) (**figure 13.16**). Abnormal chromosomes are balanced if the normal amount



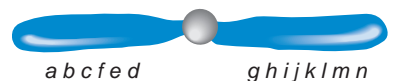
a. Normal sequence of genes



b. Deleted sequence of genes



c. Duplicated sequence of genes



d. Inverted sequence of genes

**Figure 13.16 Chromosome abnormalities.** If a hypothetical normal gene sequence appears as shown in (a), then (b) represents a deletion, (c) a duplication, and (d) an inversion.

of genetic material persists (inversions and balanced translocations) and unbalanced if excess or deficient DNA results (duplications and deletions, which may be caused by inversions or translocations).

## Deletions and Duplications

### Ashley's Story

*Our daughter, Ashley Elizabeth Naylor (figure 13.17), was born August 12, 1988. The doctors suspected complications. Two weeks after her birth, chromosome analysis revealed cri-du-chat (cat cry) syndrome, also known as 5p<sup>-</sup> syndrome because part of the short arm of one copy of chromosome 5 is missing. This is a rare disorder, we were told, and little could be offered to help our daughter. The doctors used the words "profoundly retarded."*

*Ashley defied all the standard medical labels, as well as her doctors' expectations. Her spirit and determination enabled her to walk with the aid of a walker and express herself using sign language and a communication device. With early intervention and education, Ashley found the resources and additional*



**Figure 13.17** Ashley Naylor brought great joy to her family and community during her short life. She had 5p<sup>-</sup> syndrome.

Courtesy of Kathy Naylor.

*encouragement she needed to succeed. In May of 1994, Ashley's small body could no longer support the spirit that inspired so many. She passed away after a long battle with pneumonia. Her physical presence is gone, but her message remains: hope.*

A **deletion** is missing genetic material. Deletions range greatly in size, from a few bases to large expanses of chromosomes. The larger deletions tend to have greater effects because they remove more genes. In 5p<sup>-</sup> syndrome, affected children have a high-pitched cry similar to the mewing of a cat, have pinched facial features, and are mentally retarded and developmentally delayed. Different chromosome regions cause the catlike cry, mental retardation, and developmental delay. The deletion removes the gene for telomerase reverse transcriptase, which normally keeps telomeres long in cells that divide often. The gene's absence may contribute to the shortened life span. A detailed karyotype can reveal whether a child will have only the catlike cry and perhaps poor weight gain, or will have all of the signs and symptoms, which include low birth weight, poor muscle tone, a small head, and impaired language skills.

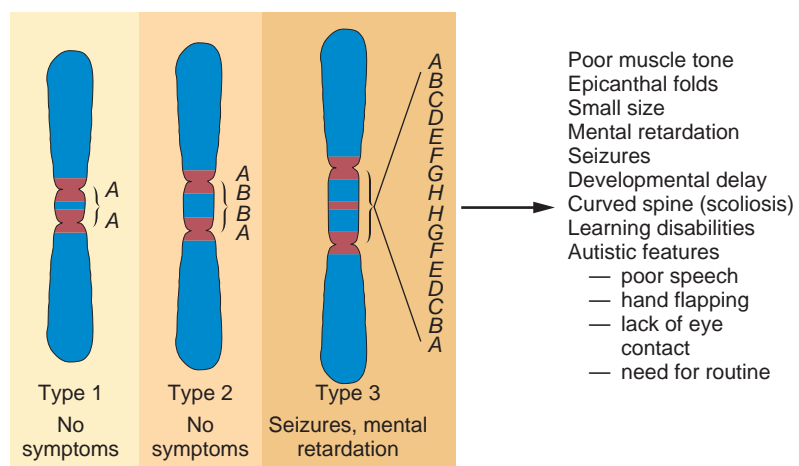
A **duplication** is a region of a chromosome where genes are repeated. Duplications, like deletions, are more likely to cause symptoms if they are extensive. For example, duplications of chromosome 15 do not produce a phenotype unless they repeat several genes. **Figure 13.18** shows three duplicated chromosome 15s, with increasing

amounts of material repeated. Many people have the first two types of duplications and have no symptoms. However, several unrelated individuals with the third, larger duplication have seizures and mental retardation. Duplications and more extensive amplifications have been very important in evolution. This is discussed in chapter 16.

FISH can detect tiny deletions and duplications that are smaller than the bands of conventional chromosome staining. However, FISH is limited to genes for which DNA probes are available—that is, known genes.

Deletions and duplications too small to be detected on karyotypes and those for which FISH probes aren't available—called microdeletions and microduplications—may also be important to health. For example, many microdeletions of the Y chromosome cause infertility. Small gains and losses of genetic material may also cause mental retardation. An underlying cause can be identified in only 50 percent of cases of mental retardation, and only about 10 percent of cases are associated with a cytogenetic abnormality large enough to visualize in a karyotype, in which the thinnest bands still represent at least 5 to 10 million bases of DNA.

Since larger deletions and duplications account for some cases of mental retardation, it is reasonable to expect that smaller gains and losses are implicated, too. To test this hypothesis, researchers did a copy number analysis (discussed in chapter 12) of the chromosomes of 100 children with mental



**Figure 13.18** A duplication. A study of duplications of parts of chromosome 15 revealed that small duplications do not affect the phenotype, but larger ones may. The letters indicate specific DNA sequences, which serve as markers to compare chromosome regions. Note that the duplication is also inverted.



retardation. Eight of the children had a deletion smaller than 178,000 bases, and two had duplications smaller than 1.1 million bases—both beneath the radar of standard karyotypes. All ten of these microdeletions or microduplications seen in the children were also absent from their parents' chromosomes. If a chromosome aberration in an offspring can also be shown in a healthy parent, then it is assumed that the unusual chromosome does not cause the medical problem. In the ten children, because the chromosome aberrations were “*de novo*”—new—they are indeed likely responsible for the mental retardation. The next steps in the research are to identify mutations in the implicated genome regions in other individuals with mental retardation, and then to search for causative genes.

Deletions and duplications can arise from chromosome rearrangements. These include translocations, inversions, and ring chromosomes.

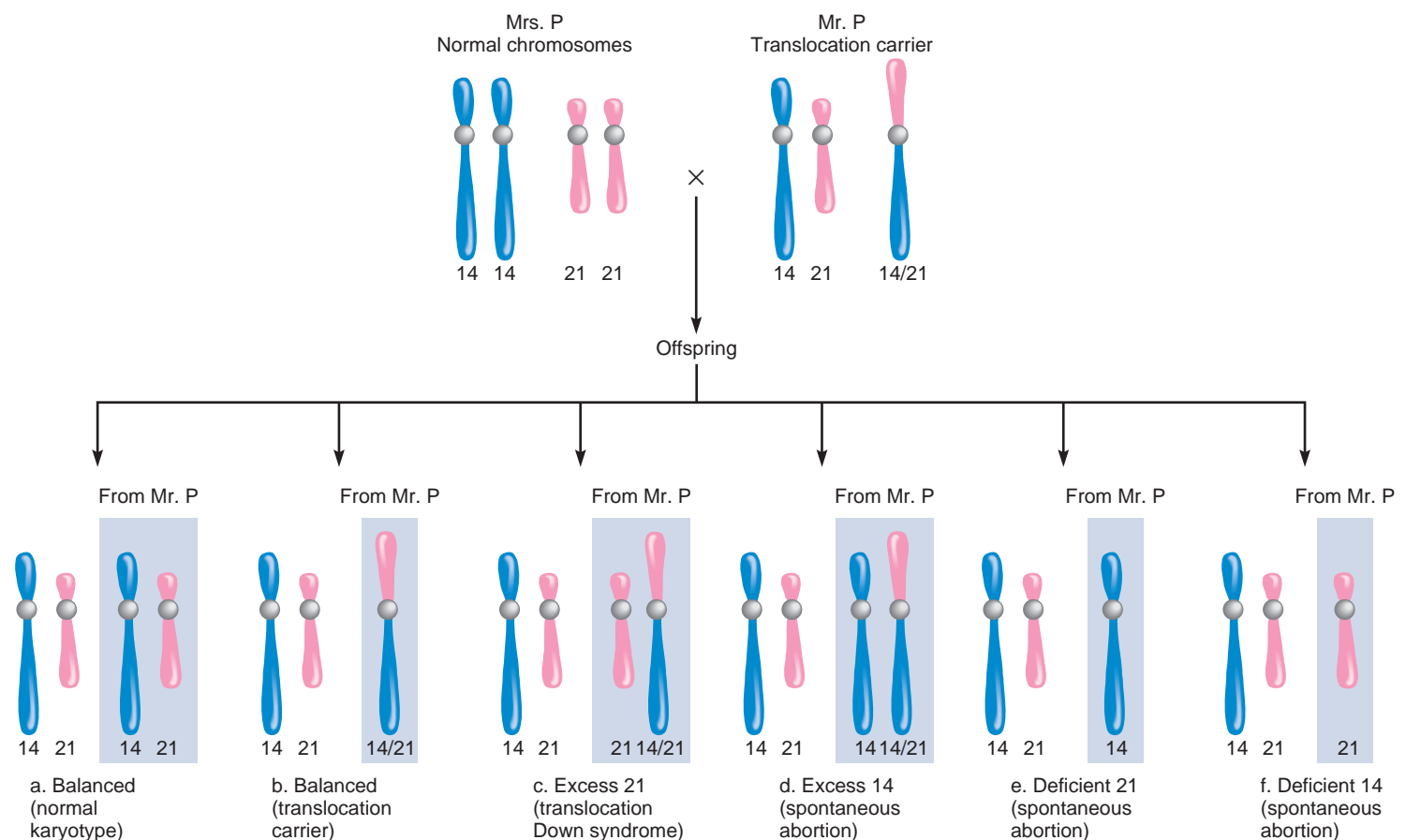
## Translocation Down Syndrome

### Rhiannon's Story

When Rhiannon P. was born, while her parents marveled at her beauty, the obstetrician was disturbed by her facial features: the broad, tilted eyes and sunken nose looked very slightly like the face of a child with Down syndrome. The doctor might not have noticed, except that the mother, Felicia, had had two spontaneous abortions. The family history suggested a chromosome problem. So when he examined the newborn, he looked for the tell-

*tale single crease in the palms of Down syndrome, and found it. Gently, he told Felicia and her husband Matt that he'd like to do a chromosome check.*

*Two days later, the new parents learned that their daughter had an unusual form of Down syndrome that was inherited from one of them, rather than the “extra chromosome” form of the condition that causes most cases. Since Matt's mother and sister had also had several miscarriages, the suspected exchanged chromosomes likely came from his side. Karyotypes of Matt and Felicia confirmed this: Matt was a translocation carrier. One of his chromosome 14s had attached to one of his chromosome 21s, and distribution of the unusual chromosome in meiosis had led to various imbalances, depicted in **figure 13.19**.*



**Figure 13.19 A Robertsonian translocation.** Mr. P. has only 45 chromosomes because the long arm of one chromosome 14 has joined the long arm of one chromosome 21. He has no symptoms. Mr. P. makes six types of sperm cells, and they determine the fates of offspring. **(a)** A sperm with one normal chromosome 14 and one normal 21 yields a normal child. **(b)** A sperm carrying the translocated chromosome produces a child who is a translocation carrier, like Mr. P. **(c)** If a sperm contains Mr. P.'s normal 21 and his translocated chromosome, the child receives too much chromosome 21 material and has Down syndrome. **(d)** A sperm containing the translocated chromosome and a normal 14 leads to excess chromosome 14 material, which is lethal in the embryo or fetus. If a sperm lacks either chromosome 21 **(e)** or 14 **(f)**, it leads to monosomies, which are lethal prenatally. (Chromosome arm lengths are not precisely accurate.)

*Rhiannon had very mild Down syndrome. She did not have any of the physical problems associated with the condition, and she did well in school with the help of a special education teacher. Matt and Felicia chose to see the bright side—each conception would have a one in three chance of having balanced chromosomes. Some day they would give Rhiannon a brother or sister.*

In a translocation, different (nonhomologous) chromosomes exchange or combine parts. Translocations can be inherited because they can be present in carriers, who have the normal amount of genetic material, but it is rearranged. A translocation can affect the phenotype if it breaks a gene or leads to duplications or deletions in the chromosomes of offspring.

There are two major types of translocations, as well as rarer types. In a **Robertsonian translocation**, the short arms of two different acrocentric chromosomes break, leaving sticky ends on the two long arms that join, forming a single, large chromosome with two long arms. The tiny short arms are lost, but their DNA sequences are repeated elsewhere in the genome, so the loss does not cause symptoms. The person with the large, translocated chromosome, called a **translocation carrier**, has 45 chromosomes, but may not have symptoms if no crucial genes have been deleted or damaged. Even so, he or she may produce unbalanced gametes—sperm or oocytes with too many or too few genes. This can lead to spontaneous abortion or birth defects.

In 1 in 20 cases of Down syndrome, a parent has a Robertsonian translocation between chromosome 21 and another, usually chromosome 14. That parent produces some gametes that lack either of the involved chromosomes and some gametes that have extra material from one of the translocated chromosomes. In such a case, each fertilized ovum has a 1 in 2 chance of ending in spontaneous abortion, and a 1 in 6 chance of developing into an individual with Down syndrome. The risk of giving birth to a child with Down syndrome is theoretically 1 in 3, because the spontaneous abortions are not births. However, because some Down syndrome fetuses spontaneously abort, the actual risk of a couple in this situation having a child with Down syndrome is about 15 percent. The other two outcomes—a fetus with normal chromosomes or a translocati-

tion carrier like the parent—have normal phenotypes. Either a male or a female can be a translocation carrier, and the condition is not related to age.

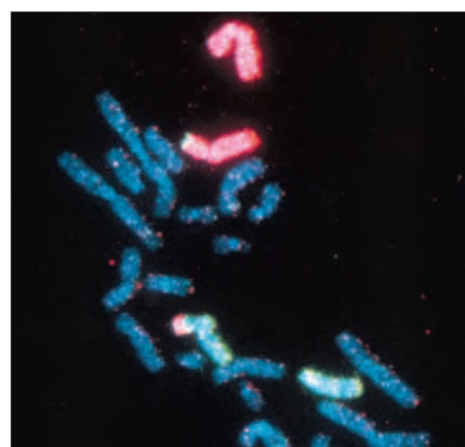
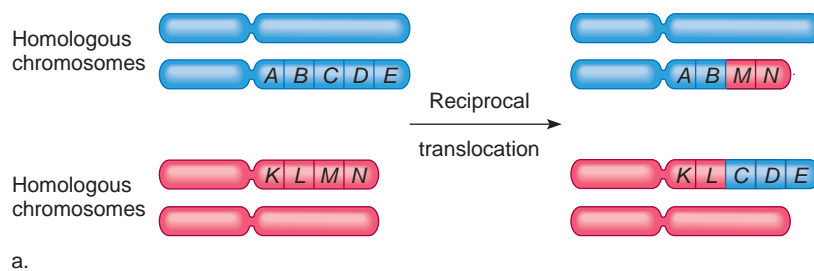
Because Robertsonian translocations are among the more common chromosomal aberrations, an intriguing idea has arisen—they could one day lead to a human karyotype of 44 instead of 46 chromosomes, and perhaps even two types of people! Individuals who have one Robertsonian translocation have 45 chromosomes, and therefore may make gametes missing a chromosome, which impairs fertility. A person who has two different Robertsonian translocations would have 44 chromosomes, but the normal amount of genetic material. Two such people could have children together, the male producing sperm and the female producing oocytes with 22 chromosomes each. Robertsonian translocations affect one in 1,000 individuals. The chance of two people with different single translocations passing both to shared offspring is about 1 in 4 million—unlikely, yet possible.

In the second major type of translocation, a **reciprocal translocation**, two different chromosomes exchange parts (**figure 13.20**). FISH can be used to highlight

the involved chromosomes. If the chromosome exchange does not break any genes, then a person who has both translocated chromosomes is healthy and a translocation carrier. He or she has the normal amount of genetic material, but it is rearranged. A reciprocal translocation carrier can have symptoms if one of the two breakpoints lies in a gene, disrupting its function. Sometimes, a *de novo* translocation arises in a gamete that leads to a new individual with a disorder, as opposed to inheriting a translocated chromosome from a parent who is a carrier.

A rare type of translocation is an insertional translocation. In this situation, a part of one chromosome inserts into a nonhomologous chromosome. As is the case for other chromosome anomalies, symptoms may result if a vital gene is disrupted or if genetic material is lost or present in excess. The chapter opener describes an insertional translocation in a young man and his sister.

A carrier of any type of translocation can produce some unbalanced gametes—sperm or oocytes that have deletions or duplications of some of the genes in the translocated chromosomes. The resulting phenotype depends upon the particular genes



**Figure 13.20 A reciprocal translocation.** In a reciprocal translocation, two nonhomologous chromosomes exchange parts. In **(a)**, genes C, D, and E on the blue chromosome exchange positions with genes M and N on the red chromosome. Part **(b)** highlights a reciprocal translocation using FISH. The pink chromosome with the dab of blue, and the blue chromosome with a small section of pink, are the translocated chromosomes.

that the chromosomal rearrangement disrupts and whether they are extra or missing. Sometimes a translocation and a deletion cause the same syndrome by affecting the same part of a chromosome.

A genetic counselor suspects a translocation when a family has a history of birth defects, pregnancy loss, and/or stillbirth. Prenatal testing may also reveal a translocation in a fetus, which can then be traced back to a parent who is a translocation carrier—or sometimes it is *de novo*.

## Inversions

### Madison's Story

*Madison and Grant were excited about getting the results of the amniocentesis—Madison had never carried a pregnancy this far before. But they grew alarmed when the doctor's office called and asked them to come in to receive the results.*

*Prepared for the worst, the couple was surprised and confused to learn that the fetus had an inverted chromosome—some of the bands that normally appear on chromosome 11 were flipped around. What did it mean? Before the genetic counselor would give them information on genes that might be affected, she advised that the parents-to-be have their chromosomes checked. Although waiting another week for the results raised their anxiety level even higher, it was worth it, because Madison had the same inversion as the fetus! Because Madison was healthy, the unusual chromosome would likely do their daughter no harm. When she was older, however, she might, like her mother, experience pregnancy loss.*

An inverted sequence of chromosome bands is associated with health effects in only 5 to 10 percent of cases, in which the inversion disrupts important genes. If neither parent has the inversion, then it arose in a gamete. Effects may depend on which genes are involved. The human genome sequence can be consulted to identify genes that might be implicated in a particular inversion.

Like a translocation carrier, an adult heterozygous for an inversion can be healthy, but have reproductive problems. One woman had an inversion in the long arm of chromosome 15 and had two spontaneous abortions, two stillbirths, and two children with multiple problems who died within

days of birth. She did eventually give birth to a healthy child. How did the inversion cause these problems?

Inversions with such devastating effects can be traced to meiosis, when a crossover occurs between the inverted chromosome segment and the noninverted homolog. To allow the genes to align, the inverted chromosome forms a loop. When crossovers occur within the loop, some areas are duplicated and some deleted in the resulting recombinant chromosomes. In inversions, the abnormal chromosomes result from the chromatids that crossed over.

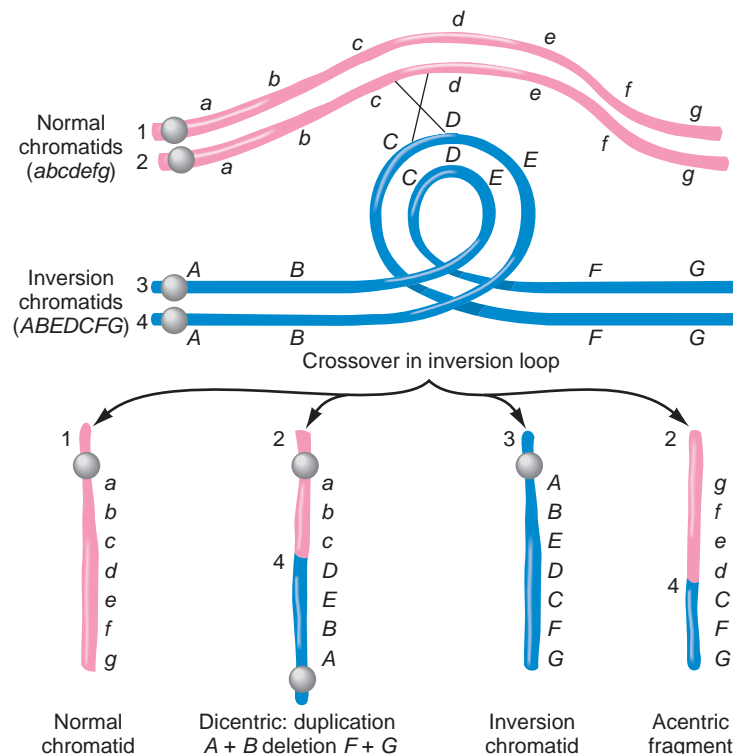
Two types of inversions are distinguished by the position of the centromere relative to the inverted section. A **paracentric inversion** does not include the centromere (**figure 13.21**). A single crossover within the inverted segment gives rise to two normal and two very abnormal chromosomes. The other two chromosomes are normal. One abnormal chromosome retains both centromeres and is termed dicentric. When the cell divides, the two centromeres are pulled to opposite sides of the cell, and the chromosome breaks, leaving pieces with

extra or missing segments. The second type of abnormal chromosome resulting from a crossover within an inversion loop is a small piece that lacks a centromere, called an acentric fragment. When the cell divides, the fragment is lost because a centromere is required for cell division.

A **pericentric inversion** includes the centromere within the loop. A crossover in it produces two chromosomes that have duplications and deletions, but one centromere each (**figure 13.22**).

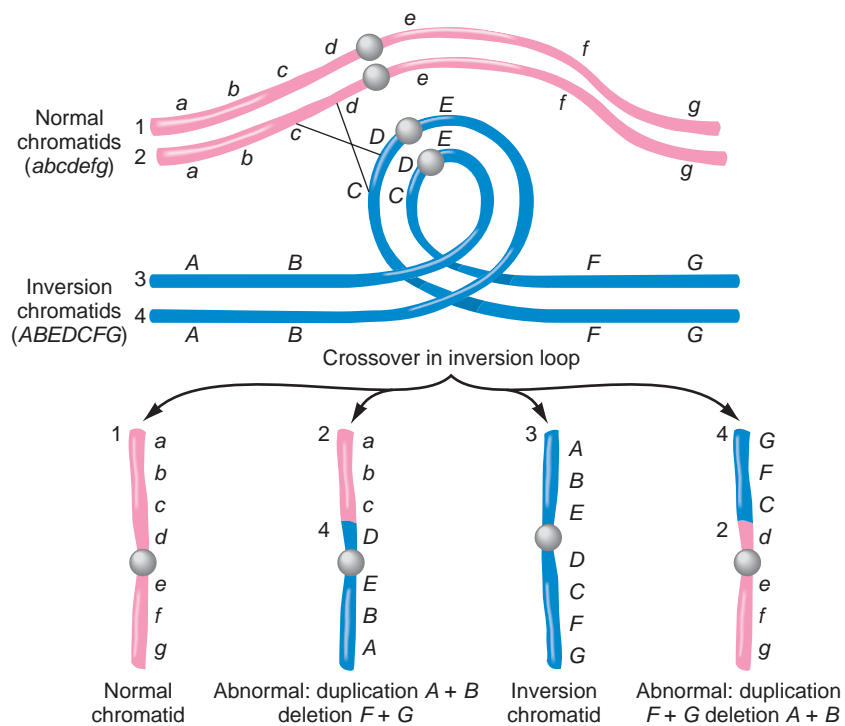
## Isochromosomes and Ring Chromosomes

Another meiotic error that leads to unbalanced genetic material is the formation of an isochromosome, which is a chromosome that has identical arms. This occurs when, during division, the centromeres part in the wrong plane (**figure 13.23**). Isochromosomes are known for chromosomes 12 and 21 and for the long arms of the X and the Y. Some women with Turner syndrome are not the more common XO, but have an isochromosome with the long

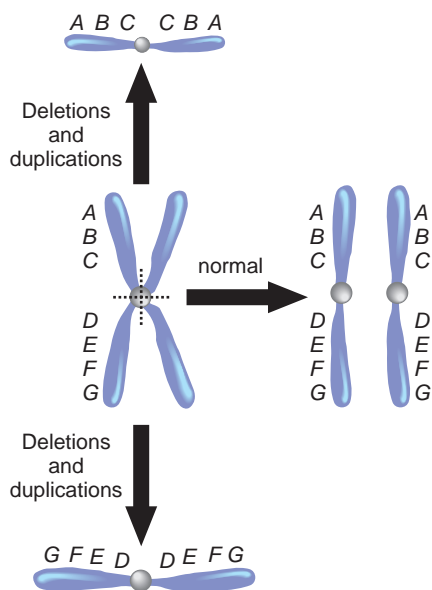


**Figure 13.21 Paracentric inversion.** A paracentric inversion in one chromosome leads to one normal chromatid, one inverted chromatid, one with two centromeres (dicentric), and one with no centromere (an acentric fragment) if a crossover occurs with the normal homolog. The letters a through g denote genes.





**Figure 13.22 Pericentric inversion.** A pericentric inversion in one chromosome leads to two chromatids with duplications and deletions, one normal chromatid, and one inverted chromatid if a crossover occurs with the normal homolog.



**Figure 13.23 Isochromosomes have identical arms.** They form when chromatids divide along the wrong plane (in this depiction, horizontally rather than vertically).

arm of the X chromosome duplicated but the short arm absent.

Chromosomes shaped like rings form in 1 out of 25,000 conceptions. Ring chromosomes may arise when telomeres are lost, leaving sticky ends that adhere. Exposure to radiation can also form rings. They can form from any chromosome, as one of the 46 chromosomes or in addition to them.

Ring chromosomes can produce symptoms when they have extra or missing genetic material. For example, a small chromosome 22 ring causes cat eye syndrome (OMIM 607576). Affected children have vertical pupils, mental retardation, heart and urinary tract anomalies, and skin growing over the anus. They have 47 chromosomes—the normal two chromosome 22s and a ring. On the other hand, a case report of a boy attributed his seizures, small head, unusual facial features, and poor blood clotting to a ring chromosome 14 missing part of the chromosome.

Ring chromosomes detected on routine amniocentesis present a challenging problem in genetic counseling, because rings usually do not affect health. Usually they consist of highly repeated DNA sequences that do not encode proteins.

Table 13.8 summarizes causes of different types of chromosomal aberrations.

**Table 13.8**

### Causes of Chromosomal Aberrations

Abnormalities	Causes
<b>Numerical Abnormalities</b>	
Polyploidy	Error in cell division (meiosis or mitosis) in which not all chromatid pairs separate in anaphase Multiple fertilization
Aneuploidy	Nondisjunction (in meiosis or mitosis) leading to lost or extra chromosomes
<b>Structural Abnormalities</b>	
Deletions and duplications	Translocation
Translocation	Crossover between a chromosome that has a pericentric inversion and its noninverted homolog
Inversion	Exchange between nonhomologous chromosomes
Dicentric and acentric	Breakage and reunion of fragment in same chromosome, but with wrong orientation
Ring chromosome	Crossover between a chromosome with a paracentric inversion and its noninverted homolog A chromosome loses telomeres and the ends fuse, forming a circle

## Key Concepts

1. Chromosome rearrangements can cause deletions and duplications.
2. In a Robertsonian translocation, the long arms of two different acrocentric chromosomes join.
3. In a reciprocal translocation, chromosomes exchange parts.
4. If a translocation leads to a deletion or duplication, or disrupts a gene, symptoms may result.
5. Gene duplications and deletions can occur in isochromosomes and ring chromosomes, and when crossovers involve inversions.
6. An isochromosome has two identical arms, introducing duplications and deletions.
7. Ring chromosomes can add genetic material.

### 13.5 Uniparental Disomy—A Double Dose from One Parent

If nondisjunction occurs in sperm and oocyte, a pair of chromosomes (or their parts) can come solely from one parent, rather than one from each parent, as Mendel's law of segregation predicts. For example, if a sperm lacking a chromosome 14 fertilizes an ovum with two copies of that chromosome, an individual with the normal 46 chromosomes results, but the two chromosome 14s come only from the female.

Inheriting two chromosomes or chromosome segments from one parent is called **uniparental disomy** (UPD) ("two bodies from one parent"). UPD can also arise from a trisomic embryo in which some cells lose the extra chromosome, leaving two homologs from one parent. For example, an embryo may have trisomy 21, with the extra chromosome 21 coming from the father. If in some cells the chromosome 21 from the mother is lost, then both remaining copies of the chromosome are from the father.

Because UPD requires the simultaneous occurrence of two very rare events—either nondisjunction of the same chromosome in sperm and oocyte, or trisomy followed by chromosome loss—it is very rare. In addition, many cases are probably never seen, because bringing together identical homologs

inherited from one parent could give the fertilized ovum a homozygous set of lethal alleles. Development would halt. Other cases of UPD may go undetected if they cause known recessive conditions and both parents are assumed to be carriers, when actually only one parent contributed to the offspring's illness. This was how UPD was discovered.

In 1988, Arthur Beaudet of the Baylor College of Medicine saw a very unusual patient with cystic fibrosis. Beaudet was comparing CF alleles of the patient to those of her parents, and he found that only the mother was a carrier—the father had two normal alleles. Beaudet constructed haplotypes for each parent's chromosome 7, which includes the CF gene, and he found that the daughter had two copies from her mother, and none from her father (**figure 13.24**). How did this happen?

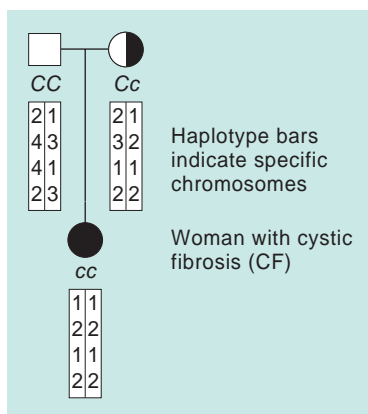
Apparently, in the patient's mother, nondisjunction of chromosome 7 in meiosis II led to formation of an oocyte bearing two identical copies of the chromosome, instead of the usual one. A sperm that had also undergone nondisjunction and lacked a chromosome 7 then fertilized the abnormal oocyte. The mother's extra genetic material compensated for the father's deficit, but unfortunately, the child inherited a double dose of the mother's chromosome that carried the mutant CF allele. In effect, inheriting two of the same chromosome from one

parent shatters the protection that combining genetic material from two individuals offers, a protection that is the defining characteristic of sexual reproduction.

UPD may also cause disease if it removes the contribution of the important parent for an imprinted gene. Recall from chapter 6 that an imprinted gene is expressed if it comes from one parent, but silenced if it comes from the other (see figure 6.16). If UPD removes the parental genetic material that must be present for a critical gene to be expressed, a mutant phenotype results. The classic example is the 20 to 30 percent of Prader-Willi syndrome and Angelman syndrome cases caused by UPD (see figure 6.17). These disorders arise from mutations in different genes that are closely linked in a region of the long arm of chromosome 15, where imprinting occurs. They both cause mental retardation and a variety of other symptoms, but are quite distinct.

In 1989, researchers found that some children with Prader-Willi syndrome have two parts of the long arm of chromosome 15 from their mothers. The disease results because the father's Prader-Willi gene must be expressed for the child to avoid the associated illness. For Angelman syndrome, the situation is reversed. Children have a double dose of their father's DNA in the same chromosomal region implicated in Prader-Willi syndrome, with no maternal contribution. The mother's gene must be present for health.

People usually learn their chromosomal makeup only when something goes wrong—when they have a family history of reproductive problems, exposure to a toxin, cancer, or symptoms of a known chromosomal disorder. While researchers analyze the human genome sequence, chromosome studies will continue to be part of medical care—beginning before birth.



**Figure 13.24 Uniparental disomy.**

Uniparental disomy doubles part of one parent's genetic contribution. In this family, the woman with CF inherited two copies of her mother's chromosome 7, and neither of her father's. Unfortunately, it was the chromosome with the disease-causing allele that she inherited in a double dose.

## Key Concepts

1. Uniparental disomy (UPD) results when two chromosomes or chromosome parts are inherited from the same parent.
2. It can arise from two nondisjunction events or a trisomy and subsequent chromosome loss.
3. UPD can cause disease if it creates a homozygous recessive condition, or if it disrupts imprinting.

# Summary

## 13.1 Portrait of a Chromosome

1. Mutation can occur at the chromosomal level. **Cytogenetics** is the study of chromosome aberrations and their effects on phenotypes.
2. **Heterochromatin** stains darkly and harbors many DNA repeats. **Euchromatin** is light staining and contains many protein-encoding genes.
3. A chromosome consists of DNA and proteins. Essential parts are the **telomeres**, **centromeres**, and origin of replication sites.
4. Centromeres include alpha satellites and centromere-associated proteins, some of which form kinetochores that contact spindle fibers. CENP-A is a protein that may control centromere duplication.
5. Subtelomeres have telomerelike repeats that gradually disappear inward toward the centromere, as protein-encoding genes predominate. Chromosomes vary in gene density.
6. Chromosomes are distinguishable by size, centromere position, satellites, DNA probes to specific sequences, and staining patterns.
7. A **karyotype** is a size-ordered chromosome chart. A **metacentric** chromosome has two fairly equal arms. A **submetacentric** chromosome has a large arm and a short arm. An **acrocentric** chromosome's centromere is near a tip, so that it has one long arm and one very short arm.

## 13.2 Visualizing Chromosomes

8. Chromosomes can be obtained from any cell that has a nucleus. Prenatal diagnostic techniques include **amniocentesis**, **chorionic villus sampling**, and fetal cell sorting.

9. Fluorescence *in situ* hybridization provides more specific chromosome bands than dyes. Ideograms are diagrams that display chromosome bands, FISH data, and gene loci.
10. Chromosomal shorthand indicates chromosome number, sex chromosome constitution, and the nature of the abnormality.

## 13.3 Abnormal Chromosome Number

11. A **euploid** somatic human cell has 22 pairs of autosomes and one pair of sex chromosomes.
12. **Polyploid** cells have extra chromosome sets.
13. **Aneuploids** have extra or missing chromosomes. **Trisomies** (an extra chromosome) are less harmful than **monosomies** (lack of a chromosome), and sex chromosome aneuploidy is less severe than autosomal aneuploidy. **Nondisjunction** is uneven distribution of chromosomes in meiosis. It causes aneuploidy. Most autosomal aneuploids cease developing as embryos. The most common at birth are trisomies 21, 13, and 18, because these chromosomes are gene-poor. Sex chromosome anomalies (45, XO; 47, XXX; 47, XXY; 48, XXYY; 47, XYY) are less severe.

## 13.4 Abnormal Chromosome Structure

14. **Deletions** and/or **duplications** can result from crossing over after pairing errors occur in synapsis. Crossing over in an inversion heterozygote can also generate deletions and duplications.
15. In a **Robertsonian translocation**, the short arms of two acrocentric chromosomes

break, leaving sticky ends on the long arms that join to form an unusual, large chromosome.

16. In a **reciprocal translocation**, two nonhomologous chromosomes exchange parts.
17. An insertional translocation places a DNA sequence from one chromosome into another, nonhomologous chromosome.
18. A **translocation carrier** may have an associated phenotype if the translocation disrupts a vital gene. A translocation carrier produces a predictable percentage of unbalanced gametes, which can lead to birth defects and spontaneous abortion if genes are missing, extra, or disrupted.
19. A heterozygote for an inversion may have reproductive problems if a crossover occurs between the inverted region and the noninverted homolog, generating deletions and duplications. A **paracentric inversion** does not include the centromere; a **pericentric inversion** does.
20. Isochromosomes repeat one chromosome arm but delete the other. They form when the centromere divides in the wrong plane during meiosis. Ring chromosomes form when telomeres are removed, leaving sticky ends that adhere.

## 13.5 Uniparental Disomy—A Double Dose from One Parent

21. In **uniparental disomy**, a chromosome, or a part of one, doubly represents one parent. It can result from nondisjunction in both gametes, or from a trisomic cell that loses a chromosome, leaving two from the same parent.
22. Uniparental disomy causes symptoms if it creates a homozygous recessive state associated with an illness, or if it affects an imprinted gene.

# Review Questions

1. What are the essential components of a chromosome? Of a centromere?
2. Which parts of chromosome structure are probably important in an evolutionary sense? What is the evidence for this?
3. How does the DNA sequence change with distance from the telomere?
4. How are centromeres and telomeres alike?
5. Distinguish among a euploid, aneuploid, and polyploid.
6. What happens during meiosis to produce
  - a. an aneuploid?
  - b. a polyploid?
  - c. the increased risk of trisomy 21 Down syndrome in the offspring of a woman over age 40 at the time of conception?
  - d. recurrent spontaneous abortions to a couple in which the man has a pericentric inversion?



- e. several children with Down syndrome in a family where one parent is a translocation carrier?
7. A human liver has patches of cells that are octaploid—that is, they have eight sets of chromosomes. Explain how this might arise.
8. Describe an individual with each of the following chromosome constitutions. Mention the person's sex and possible phenotype.
  - a. 47,XXX
  - b. 45,X
  - c. 47,XX, trisomy 21
9. Which chromosomal anomaly might you expect to find more frequently among the members of the National Basketball Association than in the general population? Cite a reason for your answer.
10. About 80 percent of cases of Edward syndrome are caused by trisomy 18; 10 percent are caused by mosaic trisomy 18, and 10 percent are attributed to translocation. Distinguish among these three chromosome aberrations.
11. List three examples illustrating the idea that the amount of genetic material involved in a chromosomal aberration affects the severity of the associated phenotype.
12. List three types of chromosomal aberrations that can cause duplications and/or deletions, and explain how they do so.
13. Distinguish among three types of translocations.
14. Why would having the same inversion on both members of a homologous chromosome pair *not* lead to unbalanced gametes, as having the inversion on only one chromosome would?
15. Define or describe the following technologies:
  - a. FISH
  - b. amniocentesis
  - c. chorionic villus sampling
  - d. fetal cell sorting
16. Why are trisomies 13 and 18 more common at birth than trisomies 5 or 16?
17. How many chromosomes would a person have who has Klinefelter syndrome and also trisomy 21?
18. Explain why a female cannot have XXY syndrome and a male cannot have XO syndrome.
19. List three causes of Turner syndrome.

## Applied Questions

1. Researchers can create “human artificial chromosomes” to study chromosome structure and function. They can build a chromosome from DNA up, or by removing material from a chromosome to see how small it can be and still function as a chromosome. Choose either approach and discuss the structures and/or DNA sequences that must be present for a chromosome to carry information and withstand the forces of cell division.
2. The following is part of a chart used to provide genetic counseling on maternal age effect on fetal chromosomes. Answer questions a–d based on this chart.
 

Maternal Age	Trisomy 21 Risk	Risk for Any Aneuploid
20	1/1,667	1/526
24	1/1,250	1/476
28	1/1,053	1/435
30	1/952	1/385
32	1/769	1/322
35	1/378	1/192
36	1/289	1/156
37	1/224	1/127
38	1/173	1/102
40	1/106	1/66
45	1/30	1/21
48	1/14	1/10

  - a. The Willoughbys have a son who has trisomy 21 Down syndrome. The mother, Suzanne, is 24 years old and pregnant. The Martinis do not have any relatives who have Down syndrome or any other chromosomal condition. Karen Martini is pregnant, and is 32 years old. Who has the lower risk of having a child with Down syndrome, Suzanne Willoughby or Karen Martini?
  - b. Why are the risks in the right-hand column higher than those in the middle column?
  - c. Sam and Alice Dekalb receive genetic counseling because of “advanced maternal age”—Alice is 40 years old. When amniocentesis reveals trisomy 13, the couple is shocked, explaining that they thought the risk of a chromosomal problem was less than 1 percent. How have they misinterpreted the statistics?
  - d. A 40-year-old woman wants to have children after she is 45. How much will her risk of conceiving a child with trisomy 21 increase in that time?
3. Amniocentesis indicates that a fetus has the chromosomal constitution 46, XX,del(5)(p15). What does this mean? What might the child's phenotype be?
4. What type of test could determine whether a triploid infant resulted from a diploid oocyte fertilized by a haploid sperm, or from two sperm fertilizing one oocyte?
5. For an exercise in a college genetics laboratory course, a healthy student constructs a karyotype from a cell from the inside of her cheek. She finds only one chromosome 3 and one chromosome 21, plus two unusual chromosomes that do not seem to have matching partners.
  - a. What type of chromosomal abnormality does she have?
  - b. Why doesn't she have any symptoms?
  - c. Would you expect any of her relatives to have any particular medical problems? If so, which medical conditions?
6. A fetus ceases developing in the uterus. Several of its cells are karyotyped. Approximately 75 percent of the cells are diploid, and 25 percent are tetraploid (four copies of each chromosome). What do you think happened? When in development did it probably occur?
7. Distinguish among Down syndrome caused by aneuploidy, mosaicism, and translocation.
8. A couple has a son diagnosed with XXY syndrome. Explain how the son's chromosome constitution could have arisen from either parent.

9. DiGeorge syndrome (OMIM 188400) causes abnormal parathyroid glands, heart defects; and an underdeveloped thymus gland. About 85 percent of patients have a microdeletion of part of chromosome 22. A girl, her mother, and a maternal aunt have very mild DiGeorge syndrome. They all have a reciprocal translocation of chromosomes 22 and 2.
  - a. How can a microdeletion and a translocation cause the same symptoms?
  - b. Why were the people with the translocation less severely affected than the people with the microdeletion?
  - c. What other problems might arise in the family with the translocation?
10. Refer to this table to answer these questions:
  - a. Which two chromosomes are out of order, and why?
  - b. Which chromosome has the greatest proportion of its DNA sequence that encodes protein?
  - c. Which chromosome has the greatest proportion of noncoding sequence?
  - d. How much larger is the largest chromosome compared to the smallest?
11. In polycystic kidney disease, cysts impair the organ's function. Several types of mutations can cause this disorder. One is a deletion in chromosome 16p13.3. Describe where this is in the genome.
12. The second most common type of Robertsonian translocation occurs between chromosomes 13 and 14. Describe the health problems of a child who inherits two full copies of chromosome 13 as well as a chromosome 14 that has some extra chromosome 13 material on it.
13. From 2 to 6 percent of people with autism have an extra chromosome that consists of two long arms of chromosome 15. The unusual chromosome includes two copies of the chromosome 15 centromere. Two normal copies of the chromosome are also present. What type of chromosome abnormality in a gamete can lead to this karyotype, which is called isodicentric 15?
14. Fetuses with trisomy 16 account for about 10 percent of pregnancy losses. However, babies with a partial trisomy 16 or who are mosaic for the extra chromosome are seen.
  - a. Why aren't babies seen with full trisomy 16?

Chromosome Number	Number of Genes	Number of Bases (in millions)
1	2,968	279
2	2,288	251
3	2,032	221
4	1,297	197
5	1,643	198
6	1,963	176
7	1,443	163
8	1,127	148
9	1,299	140
10	1,440	143
11	2,093	148
12	1,652	142
13	748	118
14	1,098	107
15	1,122	100
16	1,098	104
17	1,576	88
18	766	86
19	1,454	72
20	927	66
21	303	45
22	288	48
X	1,184	163
Y	231	51

- b. How might a partial trisomy (which is the same as a large duplication) of trisomy 16 occur?

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 13**, and **Web Activities** to find the website links needed to complete the following activities.

15. Go to the website for the Baylor College of Medicine Medical Genetics Laboratories (<http://www.bcm.edu/cma/index.htm>). Select "Reference Table," and then select "Abnormalities Detected."
  - a. Select an abnormality.
  - b. Describe the mutation at the chromosomal level.
  - c. Click on the OMIM # on the left, go to OMIM, and use the information to describe the disorder.

16. Go to the website for the Genetic Science Learning Center at the Eccles Institute of Human Genetics at the University of Utah. Follow the instructions to create a karyotype.
17. Visit the website for the Human Genome Landmarks poster. Select a chromosome, and use Online Mendelian Inheritance in Man (OMIM) to describe four traits or disorders associated with it. Or, consult the website for the Human Chromosome Launchpad for information on four genes carried on a specific chromosome.

### Case Studies and Research Results

18. The medical literature includes 18 cases of children with a syndrome consisting of poor growth before birth, developmental delay, premature puberty, loose joints, a large head, short stature, and small hands. In a different syndrome, children have a small chest, ears, and facial features as well as rib and finger defects. Children with the first condition have both copies of the entire long arm of chromosome 14 from their mothers, whereas children with the second condition inherit the same chromosome part from their fathers.
  - a. What type of chromosomal aberration is responsible for these two disorders?
  - b. Describe how each of the conditions might arise.
  - c. Describe how these conditions might result from a deletion mutation.
19. Two sets of parents who have children with Down syndrome meet at a clinic. The Phelps know that their son has trisomy 21. The Watkins have two affected children, and Mrs. Watkins has had two spontaneous abortions. Why should the Watkins be more concerned about future reproductive problems than the Phelps? How are the offspring of the two families different, even though they have the same symptoms?
20. A genome-wide scan of 291 people with mental retardation identifies four individuals who have a microdeletion in chromosome 17q21.3. The children have large noses, delayed speech, and mild mental retardation. Each had a parent with an inversion in the same part of chromosome 17.
  - a. Which arm of chromosome 17 is implicated in this syndrome?

- b. How can an inversion in a parent's chromosome cause a deletion in a child's chromosome?
- c. What other type of chromosome abnormality might occur in these children's siblings?
21. A 38-year-old woman, Dasheen, has amniocentesis. She learns that the fetus she is carrying has an inversion in chromosome 9 and a duplication in chromosome 18. She and her husband Franco have their chromosomes tested, and they learn that she has the duplication and Franco has the inversion. Both of the parents are healthy. Should they be concerned about the health of the fetus? Cite a reason for your answer.

## A Second Look

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1. What type of translocation do Esteban and Maribella have?
  2. Why doesn't their father have symptoms resulting from his abnormal chromosomes?
  3. What are two possible chromosome configurations for Marcos?
- Learn to apply the skills of a genetic counselor with additional cases found in the *Case Workbook in Human Genetics*.
- DiGeorge syndrome
  - Down syndrome
  - Tetrasomy 12p
  - Turner syndrome
  - Williams syndrome



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.



# Constant Allele Frequencies

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DNA Profiling to Identify Disaster Victims
- 14.5 Genetic Privacy

## A REVERSAL OF FORTUNE

Josiah Sutton had served 4 1/2 years of a 25-year sentence for rape when he was exonerated, thanks to a reexamination of DNA evidence. Sutton became a suspect after a woman in Houston identified him and a friend on the street five days after she had been raped, threatened with a gun, and left in a field. The two young men supplied saliva and blood samples, from which DNA profiles were done and compared to DNA profiles from semen found in the victim and in her car. At the trial, an employee of the crime lab doing the DNA analysis testified that the probability that Sutton's DNA matched that of the evidence by chance was 1 in 694,000—which led to his conviction. Jurors ignored the fact that Sutton's physical description did not match the victim's description of her assailant.

A DNA profile focuses on 13 parts of the genome that vary in most populations. On this basis, Sutton's DNA at first seemingly matched the evidence. The problem, however, wasn't in the DNA, but in the population to which it was compared. Although Sutton's pattern was rare in the general population, among black men, it wasn't—1 in 16 black men have the exact same pattern.

Sutton had asked all along for an independent DNA test, but was told he couldn't afford one. So while in prison, he read voraciously about DNA profiling, and again requested retesting, in a handwritten note. Then he got lucky. Two journalists investigating the Houston crime laboratory sent information on a few cases to a noted criminologist, who immediately saw the errors in Sutton's DNA analysis. Retesting Sutton's DNA, and comparing it to a relevant population, exonerated him.



Josiah Sutton was convicted on the basis of misinterpreted DNA evidence. A second DNA test—after he'd already served four years of a twenty-five year-prison term—led to his exoneration.

DNA profiling (originally called DNA fingerprinting) is a highly specific practical outgrowth of population genetics, a field that considers allele frequencies beyond the individual. Understanding why it is unlikely for allele frequencies to remain constant in populations over time explains much about a broader area: evolution.

So far, we've considered the gene as a "character" that transmits traits and as a biochemical blueprint for a specific protein. Inheritance is most familiar, however, at the population level.

A **population** is any group of members of the same species in a given geographical area who are potentially capable of mating and producing fertile offspring (figure 14.1). Examples of human populations are the students in a class, a stadium full of people, and the residents of a community, state, or nation. **Population genetics** is a branch of genetics that considers all the alleles in a population, which constitute the **gene pool**. The "pool" in gene pool refers to a collection of gametes, and an offspring represents two gametes from the pool. Alleles can move between populations when individuals migrate and mate. This movement, termed gene flow, underlies evolution, which is explored in the next two chapters.

It is at the population level that genetics goes beyond science, embracing information from history, anthropology, human behavior, and sociology. Population genetics enables us to trace our beginnings as well as understand our diversity today, and even predict the future. This chapter introduces the major principle underlying population genetics.

### 14.1 The Importance of Knowing Allele Frequencies

Thinking about genes at the population level begins by considering frequencies—that is, how often a particular gene variant occurs in a particular population. Such frequencies can be calculated for alleles, genotypes, or phenotypes. For example, an allele frequency for the cystic fibrosis (CF) gene might be the number of  $\Delta F508$  alleles among the residents of San Francisco.  $\Delta F508$  is the most common allele that, when homozygous, causes the disorder. The



**Figure 14.1** A population is a group of organisms of the same species living in the same place. Populations of sexually reproducing organisms include many genetic variants. This genetic diversity gives the group a flexibility that enhances species survival. To us, these hippos look alike, but they can undoubtedly recognize phenotypic differences in each other.

allele frequency derives from the two  $\Delta F508$  alleles in each person with CF, plus those carried in heterozygotes, as a proportion of all alleles for that gene in the gene pool of San Francisco. The genotype frequencies are the proportions of heterozygotes and the two types of homozygotes in the population. Finally, a phenotypic frequency is simply the percentage of people in the population who have CF (or who do not). With multiple alleles for a single gene, the situation becomes more complex because there are many more phenotypes and genotypes to consider.

Phenotypic frequencies are determined empirically—that is, by observing how common a condition or trait is in a population. These figures have value in genetic counseling in estimating the risk that a particular inherited disorder will occur in an individual when there is no family history of the illness. **Table 14.1** shows disease incidence for phenylketonuria (PKU), an inborn error of metabolism that causes mental retardation unless the person follows a special low-protein diet from birth. Note how the frequency differs in different populations.

On a broader level, shifting allele frequencies in populations reflect small steps of genetic change, called **microevolution**, that collectively constitute evolution. Genotype frequencies can change when any of the following conditions are met:

**Table 14.1**  
Frequency of PKU  
in Various Populations

Population	Frequency of PKU
Chinese	1/16,000
Irish, Scottish, Yemenite Jews	1/5,000
Japanese	1/119,000
Swedes	1/30,000
Turks	1/2,600
United States Caucasians	1/10,000

1. Individuals of one genotype are more likely to produce offspring with each other than with those of other genotypes (*nonrandom mating*).
2. Individuals *migrate* between populations.
3. Reproductively isolated small groups form within or separate from a larger population (*genetic drift*).
4. *Mutation* introduces new alleles into a population.
5. People with a particular genotype are more likely to produce viable, fertile offspring under a specific environmental condition than individuals with other genotypes (*natural selection*).

In today's world, all of these conditions, except mutation, are quite common. Therefore, genetic equilibrium—when allele frequencies are *not* changing—is rare. Put another way, given our tendency to pick our own partners and move about, microevolution is not only possible, but also nearly unavoidable. (Chapter 15 considers these factors in depth.)

When enough microevolutionary changes accumulate to keep two fertile organisms of opposite sex in a population from successfully producing fertile offspring together, **macroevolution**, or the formation of a new species, has occurred. Before we consider the pervasive genetic evidence for evolution, this chapter discusses the interesting, but unusual, situation in which certain allele frequencies stay constant, a condition called **Hardy-Weinberg equilibrium**.

## Key Concepts

1. Population genetics is the study of allele frequencies in groups of organisms of the same species in the same geographic area.
2. The genes in a population comprise its gene pool.
3. Microevolution reflects changes in allele frequencies in populations. It is not occurring if allele frequencies stay constant over generations (Hardy-Weinberg equilibrium).
4. Hardy-Weinberg equilibrium happens when mating is random and the population is large, with no migration, genetic drift, mutation, or natural selection.

## 14.2 Constant Allele Frequencies

Population genetics looks at phenotypes and genotypes among large numbers of individuals. Allele frequencies reveal the underlying rules. Tracking allele frequencies from one generation to the next can reveal evolution in action—or, if allele frequencies don't change, the state of Hardy-Weinberg equilibrium.

### Hardy-Weinberg Equilibrium

In 1908, a Cambridge University mathematician named Godfrey Harold Hardy

$p$	+	$q$	=	1		
All dominant alleles		All recessive alleles		Total number of alleles		
$p^2$	+	$2pq$	+	$q^2$	=	1
Homozygous dominant		Heterozygous		Homozygous recessive		Total number of alleles for the gene in the population

**Figure 14.2** The Hardy-Weinberg equation in English.

(1877–1947) and Wilhelm Weinberg (1862–1937), a German physician interested in genetics, independently used algebra to explain how allele frequencies can be used to predict phenotypic and genotypic frequencies in populations of diploid, sexually reproducing organisms.

Hardy unintentionally cofounded the field of population genetics with a simple letter published in the journal *Science*—he did not consider his idea to be worthy of the more prestigious British journal *Nature*. The letter began with a curious mix of modesty and condescension:

*I am reluctant to intrude in a discussion concerning matters of which I have no expert knowledge, and I should have expected the very simple point which I wish to make to have been familiar to biologists.*

Hardy continued to explain how mathematically inept biologists had incorrectly deduced from Mendel's work, that dominant traits would increase in populations while recessive traits would become rarer. This seems logical, but it is untrue, because recessive alleles are introduced by mutation or migration, maintained in heterozygotes, and increase in frequency (become more common) when they confer a reproductive advantage (natural selection). Hardy and Weinberg disproved the assumption that dominant traits increase while recessive traits decrease using the language of algebra.

The expression of population genetics in algebraic terms begins with the simple equation

$$p + q = 1.0$$

where  $p$  represents all dominant alleles for a gene, and  $q$  represents all recessive alleles. The expression " $p + q = 1.0$ " simply means that all the dominant alleles and all the

		Sperm	
		$p=A$	$q=a$
Oocytes	$p=A$	$p \times p = AA$	$p \times q = Aa$
	$q=a$	$p \times q = Aa$	$q \times q = aa$

**Figure 14.3** Source of the Hardy-Weinberg equation. A variation on a Punnett square reveals how random mating in a population in which gene A has two alleles—A and a—generates genotypes aa, AA, and Aa, in the relationship  $p^2 + 2pq + q^2$ .

recessive alleles comprise all the alleles for that gene in a population.

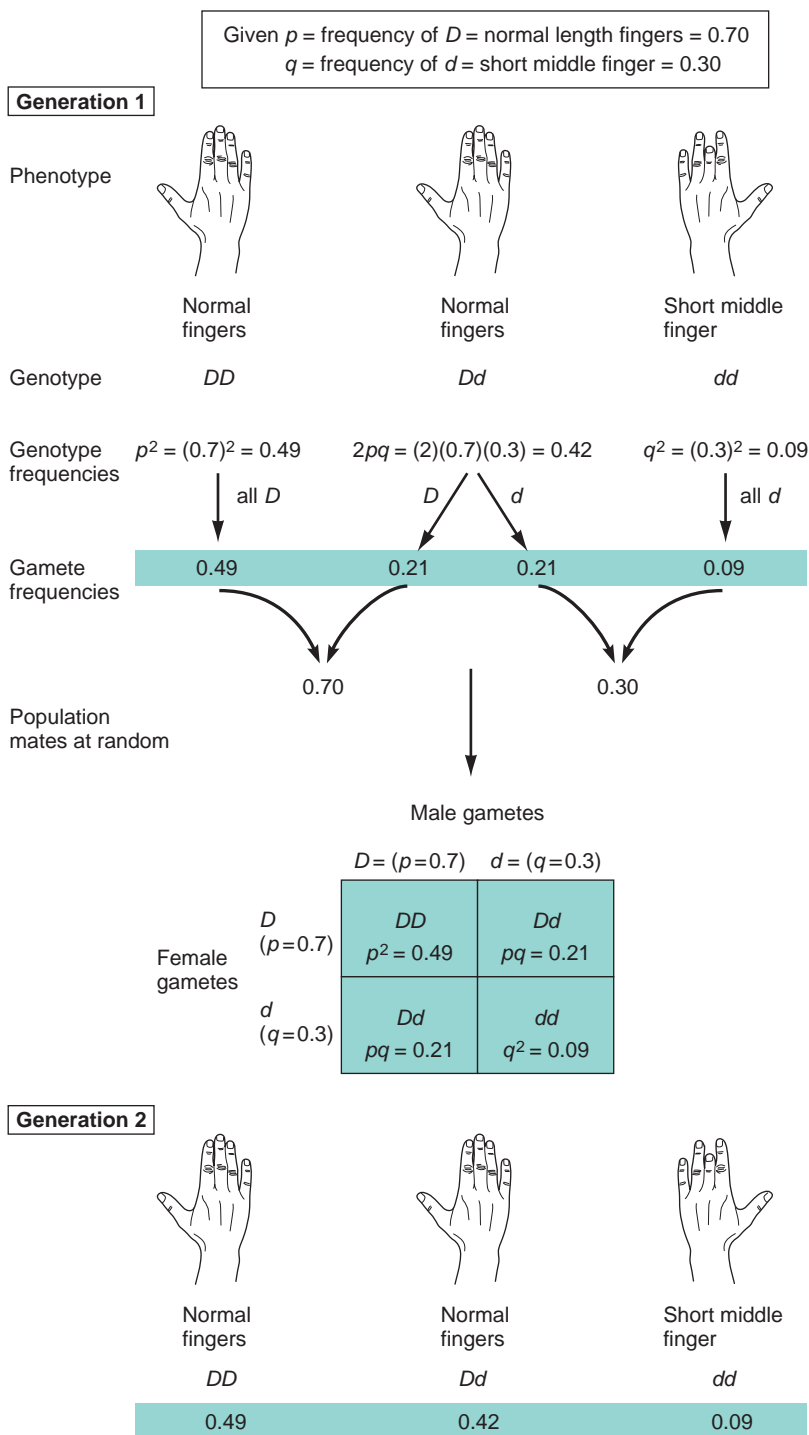
Next, Hardy and Weinberg described the possible genotypes for a gene with two alleles using the binomial expansion

$$p^2 + 2pq + q^2 = 1.0$$

In this equation,  $p^2$  represents the percentage of homozygous dominant individuals,  $q^2$  represents the percentage of homozygous recessive individuals, and  $2pq$  represents the percentage of heterozygotes (**figure 14.2**). The letter  $p$  designates the frequency of a dominant allele, and  $q$  is the frequency of a recessive allele. **Figure 14.3** shows how the binomial expansion is derived from allele frequencies. Note that the derivation is conceptually the same as tracing alleles in a monohybrid cross.

The binomial expansion used to describe genes in populations became known as the Hardy-Weinberg equation. It can reveal the changes in allele frequency that underlie evolution. If the proportion of genotypes remains the same from generation to generation, as the equation indicates, then that gene is not evolving (changing). This





**Figure 14.4 Hardy-Weinberg equilibrium.** In Hardy-Weinberg equilibrium, allele frequencies remain constant from one generation to the next.

situation, Hardy-Weinberg equilibrium, is an idealized state. It is possible only if the population is large, if its members mate at random, and if no migration, genetic drift, mutation, or natural selection takes place.

Hardy-Weinberg equilibrium is rare for protein-encoding genes that affect the phenotype, because an organism's appearance

and health affect its ability to reproduce. That is, genes that affect the phenotype are subject to natural selection—harmful allelic combinations are weeded out of the population. However, Hardy-Weinberg equilibrium is seen in DNA repeats and other sequences that do not affect the phenotype, and therefore are not subject to natural selection.

## Solving a Problem: The Hardy-Weinberg Equation

We can follow the frequency of two alleles of a particular gene from one generation to the next to understand Hardy-Weinberg equilibrium. Mendel's laws underlie such population-based calculations.

Consider an autosomal recessive trait: a middle finger shorter than the second and fourth fingers. If we know the frequencies of the dominant and recessive alleles, then we can calculate the frequencies of the genotypes and phenotypes and trace the trait through the next generation. The dominant allele  $D$  confers normal-length fingers; the recessive allele  $d$  confers a short middle finger (**figure 14.4**). We can deduce the frequencies of the dominant and recessive alleles by observing the frequency of homozygous recessives, because this phenotype—short finger—reflects only one genotype. If 9 out of 100 individuals in a population have short fingers—genotype  $dd$ —the frequency is 9/100 or 0.09. Since  $dd$  equals  $q^2$ , then  $q$  equals 0.3. Since  $p + q = 1.0$ , knowing that  $q$  is 0.3 tells us that  $p$  is 0.7.

Next, we can calculate the proportions of the three genotypes that arise when gametes combine at random:

$$\begin{aligned} \text{Homozygous dominant} &= DD \\ &= 0.7 \times 0.7 = 0.49 \\ &= 49 \text{ percent of individuals in} \\ &\text{generation 1} \end{aligned}$$

$$\begin{aligned} \text{Homozygous recessive} &= dd \\ &= 0.3 \times 0.3 = 0.09 \\ &= 9 \text{ percent of individuals in} \\ &\text{generation 1} \end{aligned}$$

$$\begin{aligned} \text{Heterozygous} &= Dd + dD \\ &= 2pq = (0.7)(0.3) + (0.3)(0.7) = 0.42 \\ &= 42 \text{ percent of individuals in} \\ &\text{generation 1} \end{aligned}$$

The proportion of homozygous individuals is calculated simply by multiplying the allele frequency for the recessive or dominant allele by itself. The heterozygous calculation is  $2pq$  because there are two ways of combining a  $D$  with a  $d$  gamete—a  $D$  sperm with a  $d$  egg, and a  $d$  sperm with a  $D$  egg.

In this population, 9 percent of the individuals have a short middle finger. Now jump

ahead a few generations, and assume that people choose mates irrespective of finger length. This means that each genotype of a female (*DD*, *Dd*, or *dd*) is equally likely to mate with each of the three types of males (*DD*, *Dd*, or *dd*), and vice versa. **Table 14.2** multiplies the genotype frequencies for each possible mating, which leads to offspring in the familiar proportions of 49 percent *DD*, 42 percent *Dd*, and 9 percent *dd*. This gene, therefore, is in Hardy-Weinberg equilibrium—the allele and genotype frequencies do not change from one generation to the next.

### Key Concepts

1. For any two alleles of a gene in a population, the proportion of homozygous dominants equals the square of the frequency of the dominant allele ( $p^2$ ), and the proportion of homozygous recessives equals the square of the frequency of the recessive allele ( $q^2$ ). The proportion of heterozygotes equals  $2pq$ .
2. The frequency of the recessive allele equals the proportion of homozygous recessives plus one-half that of carriers, and the frequency of the dominant allele equals the proportion of homozygous dominants plus one-half that of carriers.
3. In Hardy-Weinberg equilibrium, allele frequencies remain constant from one generation to the next.

### 14.3 Applying Hardy-Weinberg Equilibrium

A young woman pregnant for the first time watches a television program about cystic fibrosis. Alarmed to learn about the daily treatments and possible complications, and that CF is the most common genetic disorder in her population group (Caucasian of European descent), the woman wonders what the risk is that her child will have CF—even though there is no known history of the disorder in her or her partner’s families, which are from the same ethnic group. The Hardy-Weinberg equation can help to answer that question by determining the probability that the woman and her partner are carriers. If they are, then Mendel’s first law can be used to calculate the risk to offspring.

**Table 14.2**  
Hardy-Weinberg Equilibrium—When Allele Frequencies Stay Constant

Possible Matings		Proportion in Population	Frequency of Offspring Genotypes		
Male	Female		DD	Dd	dd
0.49 <i>DD</i>	0.49 <i>DD</i>	0.2401 ( <i>DD</i> × <i>DD</i> )	0.2401		
0.49 <i>DD</i>	0.42 <i>Dd</i>	0.2058 ( <i>DD</i> × <i>Dd</i> )	0.1029	0.1029	
0.49 <i>DD</i>	0.09 <i>dd</i>	0.0441 ( <i>DD</i> × <i>dd</i> )		0.0441	
0.42 <i>Dd</i>	0.49 <i>DD</i>	0.2058 ( <i>Dd</i> × <i>DD</i> )	0.1029	0.1029	
0.42 <i>Dd</i>	0.42 <i>Dd</i>	0.1764 ( <i>Dd</i> × <i>Dd</i> )	0.0441	0.0882	0.0441
0.42 <i>Dd</i>	0.09 <i>dd</i>	0.0378 ( <i>Dd</i> × <i>dd</i> )		0.0189	0.0189
0.09 <i>dd</i>	0.49 <i>DD</i>	0.0441 ( <i>dd</i> × <i>DD</i> )		0.0441	
0.09 <i>dd</i>	0.42 <i>Dd</i>	0.0378 ( <i>dd</i> × <i>Dd</i> )		0.0189	0.0189
0.09 <i>dd</i>	0.09 <i>dd</i>	0.0081 ( <i>dd</i> × <i>dd</i> )			0.0081
Resulting offspring frequencies:			0.49	0.42	0.09
			<i>DD</i>	<i>Dd</i>	<i>dd</i>

To derive carrier risks the Hardy-Weinberg equation is applied to population statistics on genetic disease incidence. To determine allele frequencies for autosomal recessively inherited characteristics, we need to know the frequency of one genotype in the population. This is typically the homozygous recessive class, because its phenotype indicates its genotype.

The incidence (frequency) of an autosomal recessive disorder in a population is used to help calculate the risk that a particular person is a heterozygote. Returning to the example of CF, the incidence of the disease, and therefore also of carriers, may vary greatly in different populations (**table 14.3**).

CF affects 1 in 2,000 Caucasian newborns. Therefore, the homozygous recessive frequency—*cc* if *c* represents the disease-causing allele—is 1/2,000, or 0.0005 in the population. This equals  $q^2$ . The square root of  $q^2$  is about 0.022, which equals the frequency of the *c* allele. If *q* equals 0.022, then *p*, or 1 − *q*, equals 0.978. Carrier frequency is equal to  $2pq$ , which equals (2)(0.978)(0.022), or 0.043—about 1 in 23. **Figure 14.5** summarizes these calculations.

Since there is no CF in the woman’s family, her risk of having an affected child, based on population statistics, is low. The chance of *each* potential parent being a carrier is about 4.3 percent, or 1 in 23. The chance that *both* are carriers is 1/23 multiplied by 1/23—or 1 in 529—because the probability that two independent events will occur

**Table 14.3**  
Carrier Frequency for Cystic Fibrosis

Population Group	Carrier Frequency
African Americans	1 in 66
Asian Americans	1 in 150
Caucasians of European descent	1 in 23
Hispanic Americans	1 in 46

equals the product of the probability that each event will happen alone. However, if they *are* both carriers, each of their children would face a 1 in 4 chance of inheriting the illness, based on Mendel’s first law of gene segregation. Therefore, the risk that these two unrelated Caucasian individuals with no family history of CF will have an affected child is  $1/4 \times 1/23 \times 1/23$ , or 1 in 2,116.

For X-linked traits, different predictions of allele frequencies apply to males and females. For a female, who can be homozygous recessive, homozygous dominant, or a heterozygote, the standard Hardy-Weinberg equation of  $p^2 + 2pq + q^2$  applies. However, in males, the allele frequency is the phenotypic frequency, because a male who inherits an X-linked recessive allele exhibits it in his phenotype.

The incidence of X-linked hemophilia A (see figure 6.8), for example, is 1 in 10,000 male ( $X^hY$ ) births. Therefore, *q* (the

frequency of the  $h$  allele) equals 0.0001. Using the formula  $p + q = 1$ , the frequency of the wild type allele is 0.9999. The incidence of carriers ( $X^H X^h$ ), who are all female, equals  $2pq$ , or  $(2)(0.0001)(0.9999)$ , which equals 0.00019; this is 0.0002, or 0.02 percent, which equals about 1 in 5,000. The incidence of a female having hemophilia A ( $X^h X^h$ ) is  $q^2$ , or  $(0.0001)^2$ , or about 1 in 100 million. **Figure 14.6** summarizes these calculations.

Neat allele frequencies such as 0.6 and 0.4, or 0.7 and 0.3, are unusual. In actuality, single-gene disorders are very rare, and so the  $q$  component of the Hardy-Weinberg equation contributes little. Because this means that the value of  $p$  approaches 1, the carrier frequency,  $2pq$ , is very close to  $2q$ . Thus, the carrier frequency is approximately twice the frequency of the rare, disease-causing allele.

Consider Tay-Sachs disease, which occurs in 1 in 3,600 Ashkenazim (Jewish people of eastern European descent). This means that  $q^2$  equals  $1/3,600$ , or about 0.0003. The square root,  $q$ , equals 0.017. The frequency of the dominant allele ( $p$ ) is then  $1 - 0.017$ , or 0.983. What is the likelihood that an Ashkenazi carries Tay-Sachs disease? It is  $2pq$ , or  $(2)(0.983)(0.017)$ , or 0.033. This is very close to double the frequency of the mutant allele ( $q$ ), 0.017. Modifications of the Hardy-Weinberg equation are used to analyze genes that have more than two alleles.

## Key Concepts

1. Allele frequencies in populations can be inferred from the frequency of homozygous recessive individuals ( $q^2$ ). The values of  $q$  and  $p$  can then be deduced and the Hardy-Weinberg equation applied to predict the frequency of carriers.
2. For X-linked traits, the frequency of the recessive phenotype in males is  $q$ , and in females  $q^2$ .
3. For very rare inherited disorders,  $p$  approaches 1, so the carrier frequency is approximately twice the frequency of the disease-causing allele ( $2q$ ).

## 14.4 DNA Profiling Uses Hardy-Weinberg Assumptions

Hardy-Weinberg equilibrium also applies to parts of the genome that do not affect the

### Cystic Fibrosis

incidence (autosomal recessive class) =  $1/2000 = 0.0005$

$$\therefore q^2 = 0.0005$$

$$\therefore q = \sqrt{0.0005} = 0.022$$

$$\therefore p = 1 - q = 1 - 0.022 = 0.978$$

$$\therefore \text{carrier frequency} = 2pq = (2)(0.978)(0.022) = 0.043 = 1/23$$

**Figure 14.5** Calculating the carrier frequency given population incidence: Autosomal recessive.

### Hemophilia A

incidence =  $1/10,000$  male births = 0.0001

$$\therefore q = 0.0001$$

$$\therefore p = 1 - q = 1 - 0.0001 = 0.9999$$

$$\therefore \text{carrier frequency (females)} = 2pq = (2)(0.9999)(0.0001) = 0.00019 = \text{about } 1/5000$$

$$\therefore \text{affected females} = q^2 = (0.0001)(0.0001) = 1/100 \text{ million}$$

**Figure 14.6** Calculating the carrier frequency given population incidence: X-linked recessive.



**Figure 14.7** DNA profiling detects differing numbers of repeats at specific chromosomal loci. Individuals 1 and 3 are heterozygotes for the number of copies of a 5-base sequence at a particular chromosomal locus. Individual 2 is a homozygote, with the same number of repeats on the two copies of the chromosome. (Repeat number is considered an allele.)

phenotype, and are therefore not subject to natural selection. Short repeated sequences that are not part of a protein-encoding gene fall into this category. Recall from chapter 12 that repeated sequences are scattered throughout the genome. Copy number variants (the number of copies of a particular repeat) can be followed, as if they are alleles, to identify an individual. The person is classified as a heterozygote or a homozygote based on the number of copies of the same repeat at the same chromosomal locus on the two homologs. A homozygote has the same number of repeats on both homologs, such as individual 2 in **figure 14.7**. A hetero-

zygote has two different repeat sizes, such as the other two individuals in the figure.

DNA profiling was pioneered on detecting copy number variants of very short repeats and using them to identify or distinguish individuals. In general, the technique calculates the probability that certain combinations of repeat numbers will be in two DNA sources by chance. For example, if a DNA profile of skin cells taken from under the fingernails of an assault victim matches the profile from a suspect's hair, and the chances are very low that those two samples would match by chance, that is strong evidence



Table 14.4

## Characteristics of Repeats Used in DNA Profiling

Type	Repeat Length	Distribution	Example	Fragment Sizes
VNTRs (minisatellites)	10–80 bases	not uniform	TTCGGGTTG	50–1500 bases
STRs (microsatellites)	2–10 bases	more uniform	ACTT	50–500 bases

of guilt rather than a coincidental similarity. DNA evidence is more often valuable in excluding a suspect, and should be considered along with other types of evidence.

Although obtaining a DNA profile is a molecular technique, interpreting it requires statistical analysis of population data. Two types of repeats are used in forensics and in identifying victims of disasters: **variable number of tandem repeats** (VNTRs), and **short tandem repeats** (STRs). Table 14.4 compares them.

## DNA Profiling Began with Forensics

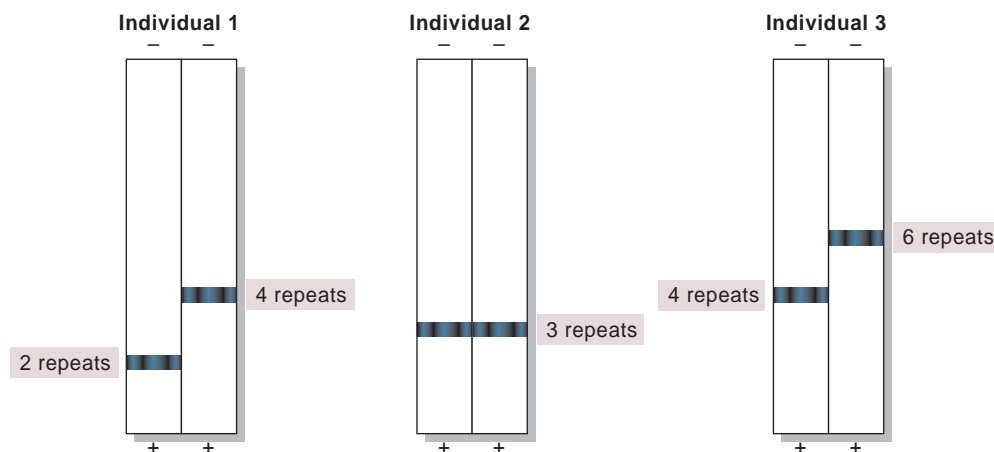
Sir Alec Jeffreys at Leicester University in the United Kingdom invented DNA profiling (then called DNA fingerprinting) in the 1980s. He detected differences in numbers of VNTRs among individuals by cutting DNA with restriction enzymes. These enzymes naturally protect bacteria by cutting foreign DNA, such as DNA from viruses, at specific short sequences. They are used as “molecular scissors” in biotechnology, as discussed

in chapter 19. Jeffreys measured DNA fragments using a technique called agarose gel electrophoresis, described in **Reading 14.1**. The different-sized fragments that result from “digesting” DNA with these enzymes are called restriction fragment length polymorphisms (RFLPs, pronounced “riflips”).

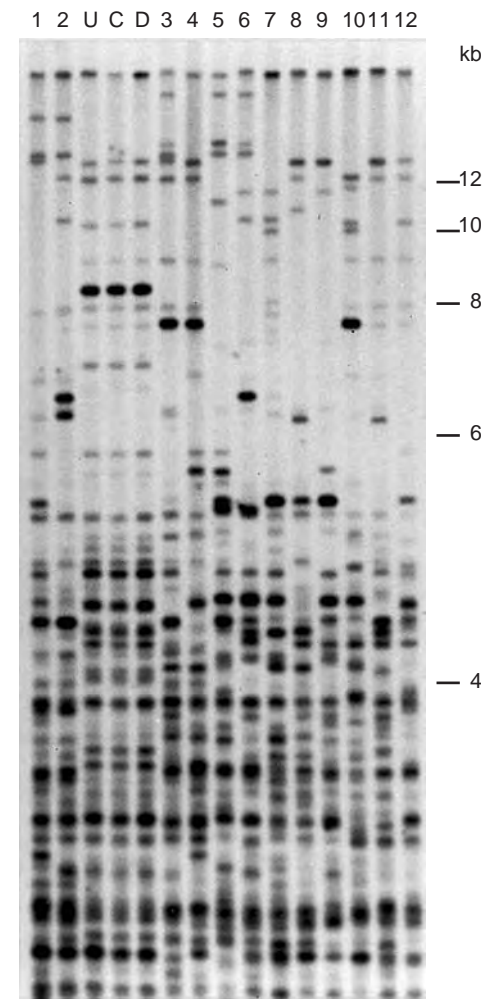
In the technique that Jeffreys used, DNA pieces migrate through a jellylike material (agarose or the more discriminating polyacrylamide) when an electrical field is applied. A positive electrode is placed at one end of the gel strip, and a negative electrode at the other. The DNA pieces, carrying negative charges because of their phosphate groups, move toward the positive pole. The pieces migrate according to size, with the shorter pieces moving faster and thus traveling farther in a given time. The pattern that forms when the different-sized fragments stop moving, with the shorter fragments closer to the positive pole and the longer ones farther away, creates a distinctive DNA pattern, or profile, that looks like a strip of black smears. An individual who is heterozygous for a repeat copy number variant will have two bands for that

locus, as shown in **Figure 14.8** for Individuals 1 and 3 from figure 14.7. A locus for which an individual is homozygous has only one corresponding band (Individual 2), because both DNA pieces are the same size.

Jeffreys’ first cases proved that a boy was the son of a British citizen so that he could enter the country, and freed a man jailed for raping two schoolgirls. Then in 1988, Jeffreys’ approach matched DNA profiles from suspect Tommie Lee Andrews’s blood cells to sperm cells left on his victim in a notorious rape case. Jeffreys also used DNA profiling to demonstrate that Dolly, the Scottish sheep, was truly a clone of the six-year-old ewe that donated her nucleus (**figure 14.9**).



**Figure 14.8 DNA profiles.** DNA fragments that include differing numbers of copies of the same repeat migrate at different speeds and stop moving at different points on a strip of polyacrylamide gel. These gels correspond to the individuals represented in figure 14.7. Actual DNA profiles typically scan 10 to 15 repeats on different chromosomes.



**Figure 14.9 Comparing DNA profiles.** These DNA profiles compare the DNA of Dolly the cloned sheep (lane D) to that of fresh donor udder tissue (U), to that of cultured donor udder tissue (C). The other twelve lanes represent other sheep. The match between Dolly and the two versions of her nucleus donor is obvious.



## Reading 14.1

# DNA Profiling: Molecular Genetics Meets Population Genetics

DNA profiling is a standard and powerful tool in forensic investigations, agriculture, paternity testing, and historical investigations. Until 1986, it was unheard of outside of scientific circles. A dramatic rape case changed that.

Tommie Lee Andrews was the first person in the United States to be convicted of a crime on the basis of DNA evidence. Andrews picked his victims months before he attacked and watched them so that he knew when they would be home alone. On a balmy Sunday night in May 1986, Andrews awaited Nancy Hodge, a young computer operator at Disney World in Orlando, Florida. The burly man surprised her when she was in her bathroom removing her contact lenses. He covered her face, then raped and brutalized her repeatedly.

Andrews was very careful not to leave fingerprints, threads, hairs, or any other indication that he had ever been in Hodge's home. But he had not counted on leaving DNA evidence. Thanks to a clear-thinking crime victim and scientifically savvy lawyers, Andrews was soon at the center of a trial—not only his trial, but one that would judge the technology that helped to convict him.

After the attack, Hodge went to the hospital, where she provided a vaginal secretion sample containing sperm. Two district attorneys who had read about DNA testing sent some of the sperm to a biotechnology company that extracted DNA and cut it with restriction enzymes. The sperm's DNA pieces were then mixed with labeled DNA probes that bound to complementary sequences.

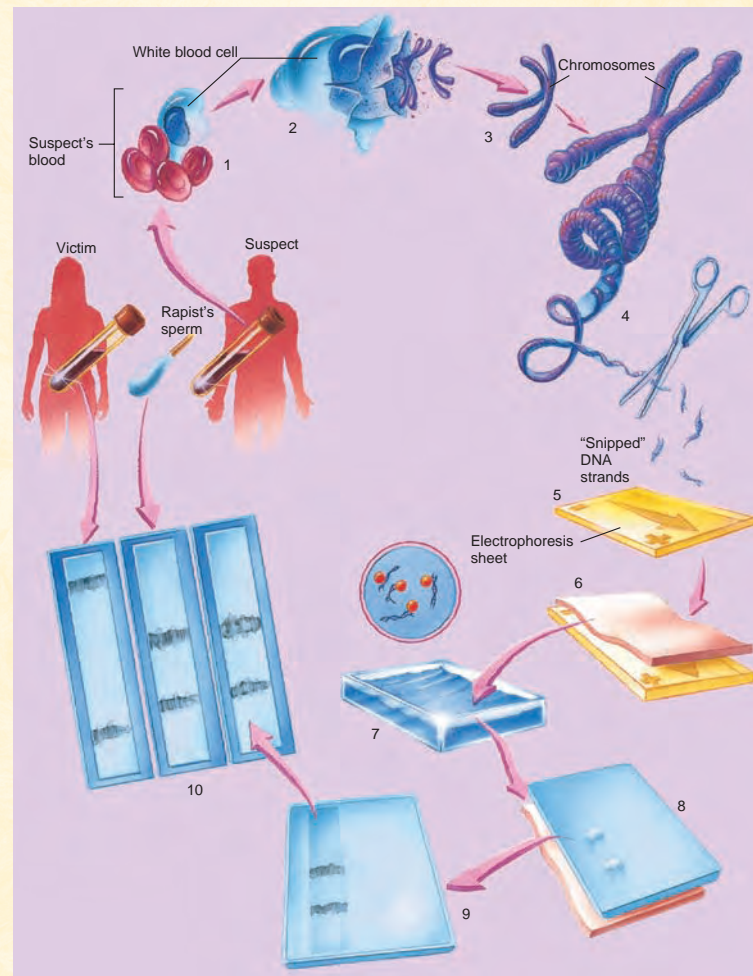
The same procedure of extracting, cutting, and probing DNA was done on white blood cells from Hodge and Andrews, who had been apprehended and held as a suspect in several assaults. When the radioactive DNA pieces from each sample, which were the sequences where the probes had bound, were separated and displayed by size, the resulting pattern of bands—the DNA profile—matched exactly for the sperm sample and Andrews's blood, differing from Hodge's DNA (**figure 1**).

Tommie Lee Andrews's allele frequencies were compared to those for a representative African American population. At his first trial in November 1987, the judge, perhaps

fearful that too much technical information would overwhelm the jury, did not allow the prosecution to cite population-based statistics. Without the appropriate allele frequencies, DNA profiling was reduced to a comparison of smeary lines on test papers to see whether the patterns of DNA pieces in the forensic sperm sample looked like those for Andrews's white blood cells. The probabilities determined from population-based statistics indicated that the possibility that Tommie Lee Andrews's DNA would match

the evidence by chance was 1 in 10 billion. But the prosecution could not mention this.

After a mistrial was declared, the prosecution cited the precedent of using population statistics to derive databases on standard blood types. So when Andrews stood trial just three months later for raping a different woman, the judge permitted population analysis. Andrews was convicted. Today, in jail, he keeps a copy of the *Discover* magazine article (written by this author) that describes his role in the first case tried using DNA profiling.



**Figure 1 DNA profiling.** A blood sample (1) is collected from the suspect. White blood cells are separated and burst open (2), releasing DNA (3). Restriction enzymes snip the strands into fragments (4), and electrophoresis aligns them by size in a groove on a sheet of gel (5). The resulting pattern of DNA fragments is transferred to a nylon sheet (6). It is then exposed to radioactively tagged probes (7) that bind the DNA areas used to establish identity. When the nylon sheet is placed against a piece of X-ray film (8) and processed, black bands appear where the probes bound (9). This pattern of bands is a DNA profile (10). It may be compared to the victim's DNA pattern, the rapist's DNA obtained from sperm cells, and other biological evidence. Today fluorescent labels are used.



Variations on DNA profiling based on sequences other than VNTRs are used when sample DNA is scarce. STRs are used when DNA is fragmented, such as in evidence from terrorist attacks and natural disasters. Their smaller size makes them more likely to persist in degraded DNA. STRs are amplified using the polymerase chain reaction (see chapter 19).

If DNA is extremely damaged, such that even STRs are obliterated, mitochondrial DNA (mtDNA) is often used instead, particularly two regions of repeats that are highly variable in populations. Because a single cell can yield hundreds or thousands of copies of the mitochondrial genome, even vanishingly small forensic samples can yield this DNA.

MtDNA analysis was critical in analyzing evidence from the September 11 terrorist attacks, most of which was extremely degraded. A more bizarre application was the case of the “voodoo child.” The evidence was a boy’s torso found floating in the River Thames in east London. The name reflects the contents of the stomach, which suggested he had been the victim of a ritualistic killing. When the DNA profile of nuclear DNA from the torso did not match that of missing English children, investigators widened the search by using a global mtDNA database. This search led to the boy’s homeland, southwestern Nigeria. He had been kidnapped, enslaved, and beheaded. Several suspects were arrested, thanks to tracking the torso to Africa.

Commercially available software enables researchers to integrate different types of DNA profiling data. For forensic applications, the FBI’s Combined DNA Index System (CODIS) shares DNA profiles electronically among local, state, and federal crime laboratories. More than 3 million DNA profiles are stored, and searching CODIS for DNA profiles has led to more than 22,000 “cold hits”—identifying a suspect from DNA alone.

Population Statistics Are Used to Interpret DNA Profiles

In forensics in general, the more clues, the better. Therefore, the power of DNA profiling is greatly expanded by tracking repeats on several chromosomes. The numbers of copies of a repeat are assigned probabilities (likelihood of being present) based on their observed frequencies in a particular population. Considering repeats on different chromosomes makes it possible to use the product rule to calculate the probabilities of particular combinations of repeat numbers occurring in a population, based on Mendel’s law of independent assortment.

The Hardy-Weinberg equation and the product rule are used to derive the statistics that back up a DNA profile. First, the pattern of fragments indicates whether an individual is a homozygote or a heterozygote for each repeat, because a homozygote only has one band representing that locus. Genotype frequencies are then calculated using parts

of the Hardy-Weinberg equation. That is,  $p^2$  and  $q^2$  denote each of the two homozygotes for a two-allele repeat, and  $2pq$  represents the heterozygote. Then the frequencies are multiplied.

Table 14.6 shows an example of multiplying frequencies of different repeat numbers. The result is the probability that this particular combination of repeat sizes would occur in a particular population. Logic then enters the equation. If the combination is very rare in the population the suspect comes from, and if it is found both in the suspect’s DNA and in crime scene evidence, such as a rape victim’s body or the stolen property in table 14.6, the suspect’s guilt appears highly likely. Figure 14.10 summarizes the procedure.

For the sequences used in DNA profiling, Hardy-Weinberg equilibrium is assumed. When it doesn’t apply, problems can arise. For example, the requirement of nonrandom mating for Hardy-Weinberg equilibrium wouldn’t be met in a community with a few very large families where distant relatives might inadvertently marry each other—a situation in many small towns. A particular DNA profile for one person might be shared by his or her cousins. In one case, a young man was convicted of rape based on a DNA profile—which he shared with his father, the actual rapist. Considering a larger number of repeat sites can guard against such complications. If more repeat sites had been considered in the rape case, chances are that they would have revealed a polymorphism that the son had inherited from his mother,

Table 14.6  
Multiplied Frequencies of Different Repeat Numbers

The Case: A famous painting has been stolen from a gallery. The thief planned the crime carefully, but as she was removing the painting from its display, she sneezed. She averted her face, but a few tiny droplets hit the wall. Detectives obtained a DNA profile using 6 repeat alleles, from different chromosomes, for DNA in nose lining cells in the droplets. Then they compared the profile to those compiled for eight people in the vicinity, all women, who had been identified by hidden camera. (Assume the suspects are in the same ethnic group.) Most of the samples matched at 2 to 4 sites, but one matched at all 6. She was the crook. Notice how the probability of guilt increases with the number of matches. Matching for the very rare allele #3 is particularly telling.

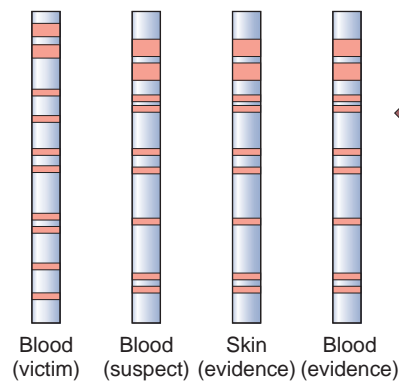
Allele	Repeat	Frequency	Cumulative Multiplied Frequencies
1	ACT on chromosome 4	1/60	
2	GGC on chromosome 17	1/24	1/60 × 1/24 = 1/1,440
3	AAGCTA on chromosome 14	1/1,200	1/1,440 × 1/1,200 = 1/1,728,000
4	GGTCTA on chromosome 6	1/11	1/1,728,000 × 1/11 = 1/19,008,000
5	ATACGAGG on chromosome 9	1/40	1/19,008,000 × 1/40 = 1/760,320,000
6	GTA	1/310	1/760,320,000 × 1/310 = 1/235,699,200,000





DNA collected from evidence at crime scene (blood, skin under victim's fingernail)

Cut, label, and probe selected DNA sequences (or use PCR)



Five specific DNA sequences from different chromosomes are labeled and separated by size

Visual match

Multiply genotype frequencies

DNA sequence 5	.60 } allele 1 .30 } allele 2	$2pq = (2)(.60)(.30) = 0.36$
DNA sequence 4	.50 } allele 1 .30 } allele 2	$2pq = (2)(.50)(.30) = 0.30$
DNA sequence 3	.15 } allele 1 .80 } allele 2	$2pq = (2)(.15)(.80) = 0.24$
DNA sequence 2	.20 }	$p^2 = (.2)^2 = 0.04$
DNA sequence 1	.80 } allele 1 .18 } allele 2	$2pq = (2)(.80)(.18) = 0.29$
$0.36 \times 0.30 \times 0.24 \times 0.04 \times 0.29 \approx 0.00031 \approx 1/3,226$		

**Conclusion:** The probability that another person in the suspect's population group has the same pattern of these alleles is approximately 1 in 3,226.

**Figure 14.10 To solve a crime.** A man was found brutally murdered, with bits of skin and blood beneath a fingernail. The bits were sent to a forensics lab as evidence, where the patterns of five DNA sequences were compared to patterns in blood from the victim as well as blood from a man being held as a suspect. The pattern for the crime scene evidence matched that for the suspect visually, but that wasn't sufficient. Allele frequencies from the man's ethnic group were used in the Hardy-Weinberg equation, yielding the probability that his DNA matched that of the skin and blood under the murdered man's fingernail by chance.

but that the father lacked. This would have indicated that the son was not guilty, but a close male relative might be.

The accuracy and meaning of a DNA profile depend upon the population that is the source for the allele frequencies. If populations are too broadly defined, then allele frequencies are typically low, leading to very large estimates of the likelihood that a suspect matches evidence based on chance. In one oft-quoted trial, the prosecutor concluded, *The chance of the DNA fingerprint of the cells in the evidence matching blood of the defendant by chance is 1 in 738 trillion*. The numbers were accurate, but some population geneticists questioned the validity of the databases. Did they really reflect the gene pool compositions of actual populations? By 1991, several judges had rejected DNA evidence because population geneticists had testified that the databases greatly oversimplify human population structure. Therefore, the odds that crime scene DNA matched suspect DNA were not as reliable as originally suggested.

The first DNA profiling databases neatly shoehorned many different groups into just three—Caucasian, black, or Hispanic—designations not necessarily biologically meaningful. People from Poland, Greece, or Sweden would all be considered white, and a dark-skinned person from Jamaica and one from Somalia would be lumped together as blacks. Perhaps the most incongruous of all were the Hispanics. Cubans and Puerto Ricans are part African, whereas people from Mexico and Guatemala have mostly Native American gene variants. Spanish and Argentinians have neither black African nor Native American genetic backgrounds. Yet these diverse peoples were considered a single population! Other groups were left out, such as Native Americans and Asians. Ultimately, analysis of these three databases revealed significantly more homozygous recessives for certain polymorphic genes than the Hardy-Weinberg equation would predict, confirming what many geneticists had suspected—allele frequencies were not in equilibrium.

Giving meaning to the allele frequencies necessary to interpret DNA profiles requires more restrictive ethnic databases. A frequency of 1 in 1,000 for a particular allele in all whites may actually be much higher or lower in, for example, only Italians, because they (and many others) tend to marry among themselves. On the other hand,

narrowly defined ethnic databases may be insufficient to interpret DNA profiles from people of mixed heritages, such as someone whose mother was Scottish/French and whose father was Greek/German.

We may need to develop mathematical models to account for real population structures. Perhaps the first step will be to understand the forces that generate genetic substructures within more broadly defined populations, which means taking into account history and human nature. Chapter 15 explores these factors.

### DNA Profiling to Identify Disaster Victims

Early editions of this textbook described using DNA profiling to identify human remains from plane crashes—then the largest application of the technology. Then terrorist attacks and natural disasters took the scope of DNA profiling to a new level.

#### Identifying World Trade Center Victims

In late September, 2001, Myriad Genetics, a company in Salt Lake City that normally provides breast cancer tests, received three unusual types of DNA samples:

- evidence from the World Trade Center
- cheek brush scrapings from relatives of people missing from the site
- “reference samples” from the victims’ toothbrushes, razors, and hairbrushes.

Technologists analyzed the DNA for copy numbers of 13 STRs as well as the sex chromosomes. The probability that any two individuals would have the same 13 markers by chance is 1 in 250 trillion. Therefore, if the STR pattern of crime scene evidence matched DNA from a victim’s toothbrush, identification was fairly certain. Myriad sent its results to the New York State Forensic Laboratory, where investigators matched family members to victims.

STR analysis worked on pieces of soft tissue, but bone bits that persisted despite the on-going fire at the site required harder mtDNA analysis. Although 20,000 tissue pieces were profiled, nearly half of the victims have not been identified. However,

new evidence is found now and then. Final demolition of a bank building in the Ground Zero area recently revealed about 700 more pieces of evidence, mostly bone bits. Evidence was also discovered, more than 5 years after the attacks, in manholes and utility areas that had not been previously checked.

DNA profiling provides much more reliable information on identity than traditional forensic identifiers such as dental patterns, scars, and fingerprints, and clues such as jewelry, wallets, and rolls of film found with the victim. Consider the case of Jose Guadalupe and Christopher Santora, two of fifteen firefighters lost from one engine company on September 11, 2001. Rescue workers brought a body found beside a firetruck next to the destroyed towers to the Medical Examiner’s office on September 13th. Other firefighters identified the remains as belonging to Guadalupe based on where the body had been found, because he had been the driver of the firetruck. The body also had a gold chain that the men recognized, and X rays revealed a birth defect in the neck bone that he was known to have had. Guadalupe was buried on October 1—but it wasn’t Guadalupe in the grave. Santora had the same necklace and the same neck condition! A DNA sample taken from the buried man’s remains and from Santora’s relatives matched.

#### Identifying Natural Disaster Victims

Different types of disasters present different challenges for DNA profiling (table 14.7 and figure 14.11). The people caught in the

Table 14.7
Challenges to DNA Profiling in Mass Disasters
<ul style="list-style-type: none"><li>• Climate that hastens decay</li><li>• Inability to reach remains</li><li>• No laboratory facilities</li><li>• Number of casualties</li><li>• Lack of relatives</li><li>• Destruction of personal item evidence</li><li>• Poor DNA quality (too fragmented, scarce, degraded)</li><li>• Lack of availability of DNA probes and statistics for population</li></ul>



**Figure 14.11 Challenges to DNA profiling.** On a small scale, such as a murder investigation, DNA profiling is enormously valuable. For large-scale disasters, many practical constraints limit the utility of the technique. The tsunami in southeast Asia in late 2004, shown here, washed away nearly all evidence; most of what little remained degraded in the heat. As a result, traditional forensic techniques, such as comparing dental records and fingerprints, proved more useful.

September 11 terrorist attacks died by fire; those caught in the Indian Ocean tsunami of 2004 or in hurricane Katrina in 2005 died by water. Whereas New York City workers searched rubble for remains, the 250,000-plus bodies strewn about by the tsunami were everywhere. Rather than hunting for tissue bits out in the open, tsunami workers had to exhume bodies that had been buried in haste to stem the spread of infectious disease. Those remains that were accessible after the waves hit quickly decayed in the hot, wet climate. These conditions, combined with the lack of roads and labs, led to 75 percent of the bodies being identified by standard dental record analysis, and 10 percent from fingerprints. Fewer than half a percent of the victims were identified by their DNA.

Forensic scientists had learned from 9/11 the importance of matching victim DNA to that of relatives, to avoid errors when two people matched at several genome sites by chance. In New York City, many of those relatives were from nearby neighborhoods; in the Asian disaster, 12 countries were directly affected and victims came from 30 countries. Entire families were washed away, leaving few and many times no relatives to provide DNA, even if everyday evidence such as toothbrushes had remained. Conditions in New Orleans were similar, but on a smaller scale. The Pakistan earthquake of 2005 combined the challenges of

the 9/11 attacks, the tsunami, and the hurricane: collecting samples for DNA profiling was very difficult.

To compensate for the barriers to implementing DNA profiling in mass disasters, Sir Alec Jeffreys advised assessing 15 to 20 repeat (copy number variant) sites, rather than the usual 13, and some investigators recommend upping the number to 50. Tragic as these disasters were, they have spurred forensic scientists to develop ways to better integrate many types of evidence, including that found in DNA sequences.

### Reuniting Holocaust Survivors

A happier use of DNA profiling is to reunite families who were torn apart in the Holocaust of World War II. The DNA Shoah project has established a DNA database of many of the 300,000 or so survivors, including some of the 10,000-plus Holocaust orphans. (*Shoah* is Hebrew for *holocaust*.) The database data are compared to DNA profiles from human remains unearthed in various building projects in parts of Europe where the mass killings occurred. The challenges in reuniting Holocaust families combine those of the 9/11 and tsunami investigations: degraded DNA and few surviving relatives and descendants. Hopefully the Shoah project will link the past to the present by matching DNA profiles.

## Key Concepts

1. DNA profiles are based on copy number variants.
2. Population statistics are applied to determine the probability that the same pattern would occur by chance in two individuals.
3. A limitation of the method is that databases may not adequately represent real populations. Developing narrower ethnic databases and considering historical and social factors may make population statistics more realistic.
4. DNA profiling of nuclear and mitochondrial DNA was performed on evidence from the September 11 terrorist attacks and the 2004 tsunami.

## 14.5 Genetic Privacy

Before the information age, population genetics was an academic discipline that was more theoretical than practical. Today, with the combination of information technology, whole genome sequencing, and shortcuts to identify people by SNP or copy number patterns, population genetics represents a powerful way to identify individuals. This new view of population genetics presents both personal and societal challenges (see Bioethics: Choices for the Future on page 277).

The human genome is 3.2 billion bits of information, each of which can be one of four possibilities—that's a huge capacity for diversity. Our genomes can vary many more ways than there are people—about 10 billion worldwide. Given these daunting numbers, one only need consider 30 to 80 genome sites to uniquely describe each person. This is why forensic tests typically only compare 10 to 15 or so loci (sites in the genome) to rule out or establish identity.

The ease of assigning highly individualized genetic nametags may be helpful in forensics, but it poses privacy issues. Consider a "DNA dragnet," a forensic approach of taking DNA profiles of all residents of a town where a violent crime is unsolved. Sir Alec Jeffreys in the U.K. conducted some of the first DNA dragnets in the late 1980s. The largest to date occurred in 1998 in Germany, where more than 16,000 men had their DNA profiled in a search for the man who raped and



## Population Biobanks

More than a dozen nations are recording and scrutinizing genetic, genealogical, life-style, and health information on their citizens to discover and archive the inherited and environmental influences on common disorders. These “biobank” projects vary in how people participate, but they raise similar concerns: Who will have access to the information? How can people benefit from providing it? How might it be abused?

The first country to systematically collect genetic information on a population level was Iceland. In 1998, a company called deCODE Genetics received government permission to collect existing health and genealogy records and to add DNA sequence data. Many Icelandic citizens can trace their families back more than a thousand years and have family tree diagrams etched in blood on old leather. Participation in the database is presumed—citizens must file a special form to opt out of the project. Despite initial concerns (mostly from outside Iceland) that the populace would feel pressured to participate, that hasn’t been the case. The head of the project claims that 95 percent of everyone who has lived in the nation since 1703, when the first census was conducted, are represented in the database.

DeCODE has used the information to identify genes that contribute to more than 25 common disorders, and is pursuing treatments for Alzheimer disease, anxiety disorder, hypertension, arthritis, heart disease, schizophrenia, stroke, and diabetes. Their strategy groups people by clinical condition and identifies parts of the genome that they uniquely share, then finds genes in these regions whose functions could explain the symptoms.

Some biobanks attempt to sample the population. The CARTaGENE project is randomly sampling 1 percent of Quebec’s citizens. Researchers in the United Kingdom are recruiting half a million individuals between the ages of 45 and 69, when many common illnesses begin, to donate DNA to a biobank. Investigators are searching for connections among DNA sequence variants, health, and lifestyle characteristics as the population ages. Unlike deCODE, the UK Biobank is run by the government.

Some projects focus on people with specific medical conditions, typically very common ones. The Estonian Genome Foundation uses registries for patients with cancer, Parkinson disease, diabetes mellitus, and osteoporosis. When patients show up for appointments, they learn about the project and are asked for details of their health histories and to donate DNA. Researchers then match variations in the DNA sequence to particular medical conditions.

Another effort, called GenomeEUtwin, has collected data on more than 600,000 pairs of twins from eight European nations for decades. The Estonian Foundation, UK Biobank, GenomeEUtwin, and CARTaGENE have formed the Public Population Project in Genomics. Their shared goal is the “creation of an open, public, and accessible knowledge database.”

The U.S. does not have a biobank, but a program called GAIN—for the Genetic Association Information Network—is similar. The project has DNA profiles (SNPs and copy number variants) from tissue sampled from 1,000 to 2,000 patients who have one of six common disorders. It is comparing these profiles to DNA profiles from the same number of healthy volunteers. The six conditions are psoriasis, schizophrenia, bipolar disorder, depression, diabetes, and attention deficit hyperactivity disorder. They were chosen based on the “highest likelihood of success” in identifying new drug targets, according to Francis Collins, who directed the human genome project.

Ideally, a biobank must meet several criteria. It should

- have data and tissue samples from at least 500,000 people.
- draw conclusions based on a population that is representative of the nation.
- have clinical information collected over many years.
- include family trees that link generations.
- compare results to those of other populations to validate DNA-disease associations.

Bioethicists have suggested strategies to ensure that individuals benefit from such projects, such as:

- Preserving choice in seeking genetic tests.
- Protecting privacy by legally restricting access to genome information.
- Tailoring genetic tests to genes that are most relevant to an individual.
- Refusing to screen for trivial traits in embryos or fetuses.

Global cooperation in establishing biobanks can tap the unique resources of different countries. For example, India and Pakistan fulfill the requirements for a useful biobank, but in addition, their cultures support consanguineous (blood relative) marriages, which has led to higher incidences of certain single-gene disorders compared to other populations. The people are splintered into many ethnic groups that suffer from unique combinations of health problems. Biobanks in India and Pakistan may hold information about diseases that could ultimately help many people.

**Table 1**

**The First Biobanks**

Biobank	Population	Website
CARTaGENE	Canada	<a href="http://www.cartagene.qc.ca/">http://www.cartagene.qc.ca/</a>
DeCODE Genetics	Iceland	<a href="http://www.decode.com/">http://www.decode.com/</a>
Estonian Genome Project	Estonia	<a href="http://www.geenivaramu.ee/index.php?show=main&amp;lang=engl">http://www.geenivaramu.ee/index.php?show=main&amp;lang=engl</a>
GenomeEUtwin	Europe	<a href="http://www.genomeutwin.org">http://www.genomeutwin.org</a>
UK Biobank	UK	<a href="http://www.ukbiobank.ac.uk/">http://www.ukbiobank.ac.uk/</a>
The Genographic Project	Anyone	<a href="https://www3.nationalgeographic.com/genographic/index.html">https://www3.nationalgeographic.com/genographic/index.html</a>



murdered an 11-year-old. The dragnet indeed caught the killer.

A more recent DNA dragnet happened in the small town of Truro, near the tip of Cape Cod, Massachusetts. Writer Christa Worthington was brutally murdered in January 2002, a knife driven completely through her heart into the floorboards, and her toddler daughter found at her side, trying to mop up the blood. Only 790 men lived in the seaside village in the winter. DNA from semen in her body did not match samples in any criminal databases. Three years later, on the advice of federal authorities, police began asking men at Truro's few winter gathering places to provide cheek swabs for DNA testing. There was no requirement to do so, but a record was being kept of all who refused,

and everyone knew it. Several citizens filed complaints with the American Civil Liberties Union, but most of Truro's male residents complied—including the trash collector who was convicted of the crime in 2006.

Genetic privacy is also an issue in health care. In some facilities, patients can meet with a geneticist and have tests, but have the results kept in a "shadow file" that is not part of the official medical record. Many people take genetic tests offered on websites. This direct-to-consumer genetic testing is discussed in chapter 20.

Legislation concerning genetic privacy in the United States is beginning to catch up with the pace of bioinformatics (the use and analysis of biological information). Some protection comes from the Health

Insurance Portability and Accountability Act (HIPAA) of 1996, which requires a patient's consent for sharing health-related information or test results. This would not apply to DNA profiles obtained in forensic investigations. More recently, the Genetic Information Nondiscrimination Act (GINA) prevents employers and health insurers from discriminating on the basis of genetic information.

## Key Concepts

1. Each person has a unique genetic signature (except multiples).
2. DNA profiling introduces privacy issues.

## Summary

1. A **population** is a group of interbreeding members of the same species in a particular area. Their genes constitute the **gene pool**.

### 14.1 The Importance of Knowing Allele Frequencies

2. Population genetics considers allele, genotype, and phenotype frequencies to reveal whether microevolution is occurring. Phenotypic frequencies can be determined empirically, then used in algebraic expressions to derive other frequencies.
3. Genotype frequencies change if migration, nonrandom mating, genetic drift, mutations, or natural selection operate. In **Hardy-Weinberg equilibrium**, frequencies are not changing.

### 14.2 When Allele Frequencies Stay Constant

4. Hardy and Weinberg proposed an algebraic equation to explain the constancy of allele frequencies. This would show why dominant traits do not increase and recessive traits do not decrease in populations. The Hardy-Weinberg

equation is a binomial expansion used to represent genotypes in a population.

5. Hardy-Weinberg equilibrium is demonstrated by following gamete frequencies as they recombine in the next generation. In equilibrium, these genotypes remain constant if evolution is not occurring. When the equation  $p^2 + 2pq + q^2$  represents a gene with one dominant and one recessive allele,  $p^2$  corresponds to the frequency of homozygous dominant individuals;  $2pq$  stands for heterozygotes; and  $q^2$  represents the frequency of the homozygous recessive class. The frequency of the dominant allele is  $p$ , and of the recessive allele,  $q$ .

### 14.3 Applying Hardy-Weinberg Equilibrium

6. If we know either  $p$  or  $q$ , we can calculate genotype frequencies, such as carrier risks. Often such information comes from knowing the  $q^2$  class, which corresponds to the frequency of homozygous recessive individuals in a population.

7. For X-linked recessive traits, the mutant allele frequency for males equals the trait frequency. For very rare disorders or traits, the value of  $p$  approaches 1, so the carrier frequency ( $2pq$ ) is approximately twice the frequency of the rare trait ( $q$ ).

### 14.4 DNA Profiling Is Based on Hardy-Weinberg Assumptions

8. Repeats (**VNTRs** and **STRs**) that do not encode protein are presumably in Hardy-Weinberg equilibrium and can be compared to establish individual DNA profiles.
9. To obtain a **DNA profile**, determine repeat numbers (using RFLPs or PCR) and multiply population-based allele frequencies to derive the probability that profiles from two sources match by chance.

### 14.5 Genetic Privacy

10. People vary genetically in more ways than there are people.
11. Individuals can be distinguished genetically, introducing privacy concerns about identifying people using genetic information.

## Review Questions

1. What is a population? List three populations.
2. "We like him, he seems to have a terrific gene pool," say the parents upon meeting their daughter's boyfriend. Why doesn't their statement make sense?
3. Explain the differences among an allele frequency, a phenotypic frequency, and a genotypic frequency.
4. What does Hardy-Weinberg equilibrium mean?
5. Why is Hardy-Weinberg equilibrium more a theoretical state than a common, real situation for genes that affect the phenotype?

- What are the conditions under which Hardy-Weinberg equilibrium cannot be met?
- Why is knowing the incidence of a homozygous recessive condition in a population important in deriving allele frequencies?
- For a forensics case, why would tracking VNTR sequences provide a more reliable identification than tracking STRs?
- Why are specific population databases needed to interpret DNA profiles?
- How is the Hardy-Weinberg equation used to predict the recurrence of X-linked recessive traits?
- What is the basis of assigning a probability value to a particular copy number variant?
- Under what circumstances is analysis of repeats in mtDNA valuable?
- Describe the following ways to identify or distinguish among individuals at the DNA level:
  - VNTRs
  - STRs
  - SNPs (see chapters 7 and 12)
  - mtDNA
  - RFLPs
- Why do forensic scientists using DNA profiling have to be extra careful in their analyses when the victim and suspect are blood relatives?
- How did the challenges differ for profiling DNA in evidence from the September attacks, the 2004 tsunami, and in matching Holocaust victims to survivors?
- Suggest a novel use of DNA profiling.

## Applied Questions

- Give three examples of how population genetics can be observed in everyday life.
- Why are Hardy-Weinberg calculations more complicated if a gene has many alleles that affect the phenotype?
- How can evolution occur at a microscopic and macroscopic level?
- Two couples want to know their risk of conceiving a child with cystic fibrosis. In one couple, neither partner has a family history of the disease; in the other, one partner knows he is a carrier. How do their risks differ?
- How does calculation of allele frequencies differ for an X-linked trait or disorder compared to one that is autosomal recessive?
- Why might understanding Hardy-Weinberg equilibrium be important in understanding epidemiology (the patterns of infectious diseases in populations)?
- Profiling of Y chromosome DNA implicated Thomas Jefferson in fathering a child of his slave, discussed in chapter 1. What might have been a problem with the conclusion?
- Glutaric aciduria type I (OMIM 231680) causes progressive paralysis and brain damage. It is very common in the Amish of Lancaster County, Pennsylvania—0.25 percent of newborns have the disorder. What percentage of newborns are carriers for this condition?
- Torsion dystonia (OMIM 128100) is a movement disorder that affects 1 in 1,000 Jewish people of eastern European descent (Ashkenazim). What is the carrier frequency in this population?
- The Finnish population has a 1 percent carrier frequency for a seizure disorder called myoclonus epilepsy (OMIM 607876). Two people who have no relatives with the illness ask a genetic counselor to calculate the risk that they will conceive an affected child, based on their belonging to this population group. What is the risk?
- Maple syrup urine disease (MSUD) (see Reading 2.1) is autosomal recessive and causes mental and physical retardation, difficulty feeding, and a sweet odor to urine. In Costa Rica, 1 in 8,000 newborns inherits the condition. What is the carrier frequency of MSUD in this population?
- The amyloidoses are a group of inborn errors of metabolism in which sticky protein builds up in certain organs. Amyloidosis caused by a mutation in the gene encoding a blood protein called transthyretin (OMIM 176300) affects the heart and/or nervous system. It is autosomal recessive. In a population of 177 healthy African Americans, four proved, by blood testing, to have one mutant allele of the transthyretin gene. What is the carrier frequency in this population?
- Ability to taste phenylthiocarbamide (PTC) (OMIM 607751) is mostly determined by the gene *PTC*. The letters *T* and *t* are used here to simplify analysis. *TT* individuals taste a strong, bitter taste; *Tt* people experience a slightly bitter taste; *tt* individuals taste nothing.  
  
A fifth-grade class of 20 students tastes PTC that has been applied to small pieces of paper, rating the experience as “very yucky” (*TT*), “I can taste it” (*Tt*), and “I can’t taste it” (*tt*). For homework, the students test their parents, with these results:  
  
Of 6 *TT* students, 4 have 2 *TT* parents; and two have one parent who is *TT* and one parent who is *Tt*.  
  
Of 4 students who are *Tt*, 2 have 2 parents who are *Tt*, and 2 have one parent who is *TT* and one parent who is *tt*.  
  
Of the 10 students who can’t taste PTC, 4 have 2 parents who also are *tt*, but 4 students have one parent who is *Tt* and one who is *tt*. The remaining 2 students have 2 *Tt* parents.  
  
Calculate the frequencies of the *T* and *t* alleles in the two generations. Is Hardy-Weinberg equilibrium maintained, or is this gene evolving?
- DNA dragnets have been so successful in catching criminals in several countries that some people in law enforcement have suggested storing DNA samples of everyone at birth, so that a DNA profile could be obtained from anyone at any time. Do you think that this is a good idea or not? Cite reasons for your answer.

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study**, chapter 14, and **Web Activities** to find the website links needed to complete the following activities.

- On December 5, 1984, Theresa Fusco was raped and strangled near a roller-skating rink on Long Island, New York. Two similar crimes had occurred in previous months. Three young men were charged with the crime and then convicted, but proclaimed their innocence, maintaining that their confessions had been coerced and witnesses had lied. At their trial in 1990, defense lawyers requested DNA



profiling, but the judge ruled that the technology was too unproven to use. In 2003, the case was reopened. Stored semen was taken from the “rape kit” and DNA profiled, leading to exoneration. The men had not killed Theresa Fusco but they had spent more than a decade in prison.

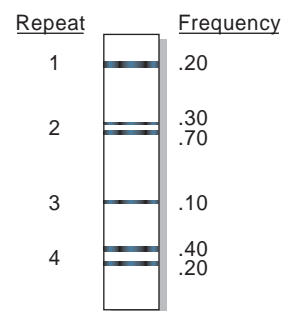
- Why might the judge have refused to consider DNA testing in 1990?
  - List the types of cells that could have been used to settle this case.
  - What information on the three suspects would be needed to interpret DNA patterns?
  - Do you think it is fair to decide whether or not a science-based forensic test or tool can be used based on how well a judge, jury, lawyers, or the public—who may have little or no training in genetics—understands how it works?
  - In 1992, lawyers Barry Scheck and Peter Neufeld, of the Cardozo School of Law in New York City, founded the nonprofit Innocence Project, a legal clinic that reopens cases where DNA profiling could have influenced the verdict. They have vindicated nearly 200 individuals. Consult the Innocence Project website, click on “Case Profiles,” and select a case, describing how the DNA evidence exonerated a prisoner.
- Go to the website for the Council for Responsible Genetics (<http://www.gene-watch.org>) and locate an article about potential misuse of genetic information in a forensic case. Describe the case, including the cell types used for DNA profiling.
  - Go to a news website and describe how DNA profiling was used in a criminal investigation or to identify the victims of an accident or disaster.
  - Go to one of the biobank websites and describe a medical test or treatment that may be developed from its data.

## Case Studies and Research Results

- An extra row of eyelashes is an autosomal recessive trait that occurs in 900 of the 10,000 residents of an island in the south Pacific. Greta knows that she is a heterozygote for this gene, because her eyelashes are normal, but she has an affected parent. She wants to have children with a homozygous dominant man, so that the trait will not affect her offspring. What is the probability that a person with normal eyelashes in this population is a homozygote for this gene?
- “Indirect genetic kinship analysis” is routinely used in forensic investigations of natural or manmade disasters. It uses a DNA profile for one person to lead to identification of a blood relative. For example, if 11 of the 13 STR alleles typically examined closely matched for a man whose brother was missing at the World Trade Center and a bone bit found there, the bone was assumed to have been from the brother. This approach is also being tried in criminal investigations. If a “cold hit” leads to a prisoner who couldn’t possibly have committed a crime (perhaps because he was locked up at the time), detectives investigate his closest relatives. Do you think that this is an ethical use of DNA profiling? What are the pros and cons of this approach?
- Rufus the cat was discovered in a trash can by his owners, his body covered in cuts and bite marks and bits of gray fur clinging to his claws—gray fur that looked a lot like the coat of Killer, the huge, aptly-named hound next door. Fearful that Killer might attack their other felines, Rufus’s distraught owners brought his body to a vet, demanding a forensic analysis. The vet suggested that the hair might have come from a squirrel, but agreed to send appropriate samples to a veterinary genetic testing laboratory.  
Identify the samples that the vet might have sent, and what information each

could contribute to the case. (P.S.: This is a real case. Killer—not his real name—was found guilty on the basis of DNA testing, but was not punished because there were no human eyewitnesses. Rufus’s angry owners installed a fence.)

- In a true crime that took place in Israel, a man knocked a woman unconscious with a cement block and then raped her. He was careful not to leave any hairs at the crime scene. But he left behind eyeglasses with unusual frames, and an optician helped police locate him. The man also left a half-eaten lollipop at the scene. DNA from blood taken from the suspect matched DNA from cheek-lining cells collected from the base of the telltale lollipop at four repeat loci on different chromosomes. Allele frequencies from the man’s ethnic group in Israel are listed beside the profile pattern below:



- For which of the tested repeats is the person a homozygote? How do you know this?
- What is the probability that the suspect’s DNA matches that of the lollipop rapist by chance? (Do the calculation.)
- The man’s population group is highly inbred—many people have children with relatives. How does this information affect the accuracy or reliability of the DNA profile? (P.S.—He was so frightened by the DNA analysis that he confessed!)

## A Second Look

- How can the same DNA profile lead to different conclusions?
- What can be done to avoid human error in interpreting DNA profiling data?
- What are two ways that the standard DNA profiling of 13 loci can be made more specific?

Learn to apply the skills of a genetic counselor with this additional case found in the *Case Workbook in Human Genetics*:

The Ice Maiden



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Changing Allele Frequencies

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- 15.4 Mutation
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  - Tuberculosis Ups and Downs—and Ups
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- 15.6 Putting It All Together: PKU Revisited

## THE EVOLUTION OF LACTOSE TOLERANCE

For millions of people who have lactose intolerance, dairy food causes cramps, bloating, gas, and diarrhea. Production of lactase, an enzyme secreted in the small intestine, declines from early childhood. It breaks down the milk sugar lactose.

Gene sequencing suggests why lactose intolerance is very common in some populations but not in others. For four linked genes on chromosome 7 that regulate digestion of the milk components lactose and calcium, variants are distinctly different in populations where most people *can* digest dairy. According to our genes, inability to digest lactose is the more ancient, wild type condition.

The alleles enabling adults to digest milk likely arose by chance, perhaps in Turkey or the Ural mountains of western Russia, according to clues in DNA sequences. (The more variable the milk-digesting gene variants on chromosome 7, the more time has elapsed, and the more ancient the people.) These people migrated to Europe between 3,500 and 6,600 years ago. When they introduced herding and therefore dairy foods, individuals with milk-tolerant alleles were healthier, leaving more children—many of whom could digest milk. Over time, populations that drank milk accumulated the lactose-tolerant alleles; those that did not, such as in Asia and Africa, continued to have many people who could not digest milk. Their genotype was not a handicap because milk was not a dietary staple.

The ability to digest milk has arisen independently in different places. Lactose intolerance is variable in ethnic populations in the United States today. Asian-Americans are 90 percent lactose intolerant; African-Americans, 75 percent; Native Americans 75 percent; and European-Americans, 10 percent.



The ability to digest lactose (milk sugar) became more prevalent in populations after agriculture introduced dairy foods—thanks to evolution.

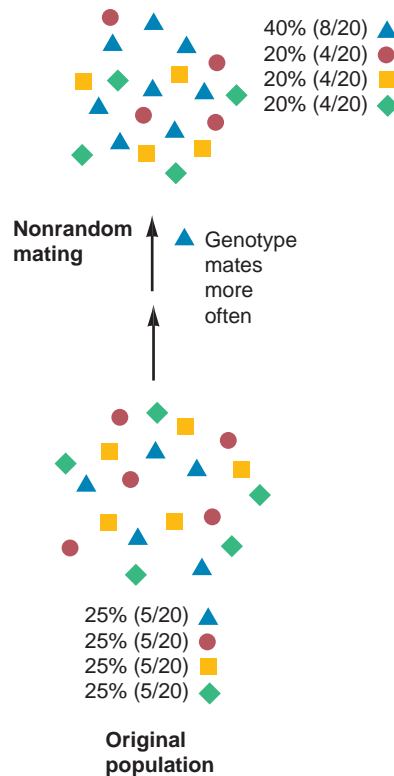
Historically, we seem to have gone out of our way to ensure that the very specific conditions necessary for Hardy-Weinberg equilibrium—unchanging allele frequencies from generation to generation—do not occur, at least for some genes. Wars and persecution kill certain populations. Economic and political systems enable some groups to have more children. Religious restrictions and personal preferences guide our choices of mates. We travel, shuttling genes in and out of populations. Natural disasters and new diseases reduce populations to a few individuals, who then rebuild their numbers, at the expense of genetic diversity. These factors, plus mutation and a reshuffling of genes at each generation, make a gene pool very fluid.

The ever-present and interacting forces of nonrandom or selective mating, migration, genetic drift, mutation, and natural selection work to differing degrees to shape populations at the allele level. Changing allele frequencies can change genotype frequencies—which in turn can change phenotype frequencies. In a series of illustrations throughout this chapter, colored shapes represent individuals who have specific genotypes. Figure 15.13 then combines the illustrations to summarize the chapter.

## 15.1 Nonrandom Mating

In the theoretical state of Hardy-Weinberg equilibrium, individuals of all genotypes are presumed equally likely to mate and to choose partners at random. For some traits this is true—we do not choose partners based on blood type, for example—but other traits do influence our mate choices. We choose partners based on physical appearance, ethnic background, intelligence, and shared interests. We marry people similar to ourselves about 80 percent of the time. Worldwide, about one-third of all marriages occur between people who were born fewer than ten miles apart! This nonrandom mating is a major factor in changing allele frequencies in human populations.

Nonrandom mating occurs when certain individuals contribute more to the next generation than others (**figure 15.1**). This is common in agriculture when semen from one prize bull is used to inseminate



**Figure 15.1 Nonrandom mating alters allele frequencies.** The different-colored shapes represent individuals with distinctive genotypes. If Hardy-Weinberg equilibrium exists for these genes in this population, then the percentages will remain the same through the generations. However, the blue triangle genotype is more reproductively successful, skewing the allele frequencies in the next generation.

thousands of cows, or a field of genetically identical crops planted. Such an extreme situation can arise in a human population when a man fathers many children. A striking mutation can reveal such behavior. In the Cape population of South Africa, for example, a Chinese immigrant known as Arnold had a very rare dominant mutation that causes teeth to fall out before age 20. Arnold had seven wives. Of his 356 living descendants, 70 have the dental disorder. The frequency of this allele in the Cape population is exceptionally high, thanks to Arnold.

The high frequency of autosomal recessive albinism among Arizona's Hopi Indians also reflects nonrandom mating. Albinism is uncommon in the general U.S. population, but it affects 1 in 200 Hopi Indians. The reason for the trait's prevalence is cultural—men with albinism often stay back



**Figure 15.2 A prevalent Y.** Genghis Khan left his mark on many men in the form of his Y chromosome. Rape of women on a sweeping scale spread the chromosome in certain Asian populations.

and help the women, rather than risk severe sunburn in the fields with the other men. They contribute more children to the population because they have more contact with the women.

The events of history reflect nonrandom mating patterns. When a group of people is subservient to another, genes tend to “flow” from one group to the other as the males of the ruling class have children with females of the underclass—often forcibly. Historical records and DNA sequences show this directional gene flow phenomenon. For example, Y chromosome analysis reveals that Genghis Khan, a Mongolian warrior who lived from 1162 to 1227, was so attentive to his many wives that today, 1 in every 200 males living between Afghanistan and northeast China shares his Y—that's 16 million men (**figure 15.2**)! Gene pools are still changed intentionally by mass rape. *In Their Own Words* on page 283 lets some of the victims speak.

Despite our partner preferences, many traits do mix randomly in the next generation. This may be because we are unaware



### Genocide by Rape in Sudan

Rape can be considered an example of non-random mating, since one person overpowers another. When one group of males rapes a particular group of females with the intent to dilute the victims' "race" (gene pool) while bolstering numbers of their own, the forced nonrandom mating becomes genocide. One of the places where this is happening today is Darfur, in western Sudan. Since 2003, Arab militia called the Janjawid ("a man with a horse and a gun") have systematically attacked black Africans, killing men and children, and repeatedly raping women. Women permitted to live after rape have their thighs slashed, so others will see their taint. Those who conceive are ostracized, for the people believe that pregnancy cannot result from rape, and the women have been promiscuous with the enemy.

Here, in their own words to Amnesty International, are views from women in Darfur:

**I was with another woman, Aziza, aged 18, who had her stomach slit on the night we were abducted. She was pregnant and was killed as they said: "It is the child of an enemy."**

**—a woman of Irenga ethnicity from the Village of Garsila**

**After six days some of the girls were released. But the others, as young as eight years old, were kept there. Five to six men would rape us in rounds, one after the other for hours during six days, every night. My husband could not forgive me after this, he disowned me.**

**—S., from Silaya, who was five months pregnant when she was raped**

**—soldiers arrived by car, camels and horses. . . . Some fifteen women and girls who had not fled quickly enough were raped in different huts in the village. The Janjawid broke the limbs . . . of some women and girls to prevent them from escaping.**

**—N., from Um Baru**

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The situation in Darfur is not unique. Similar genocide by rape has been ongoing in the eastern Democratic Republic of the Congo since 1996. Husbands flee; children are killed for defending their mothers; girls and women are serially raped, then injured or killed. Both in Darfur and the Congo, the conquerors have claimed that their intent is to diminish the genetic contributions of their victims and spread their own genes (figure 1).



**Figure 1** This Sudanese woman is lucky—she has escaped the violence of her homeland for a refugee camp in eastern Chad.

To learn more and to help, see [www.womenforwomen.org](http://www.womenforwomen.org).

of these characteristics or because we do not consider them in choosing partners. In populations where AIDS is extremely rare or nonexistent, for example, the two mutations that render a person resistant to HIV infection are in Hardy-Weinberg equilibrium. This would change, over time, if HIV arrives, because the people with these mutations would become more likely to survive to produce offspring—some of whom would perpetuate the protective mutation. Natural selection would intervene, ultimately altering allele frequencies.

Many blood types are in Hardy-Weinberg equilibrium because we do not choose partners by blood type. Yet sometimes the opposite occurs. People with mutations in the same gene meet when their families

participate in programs for people with the associated disorder. For example, more than two-thirds of relatives visiting a camp for children with cystic fibrosis are likely to be carriers, compared to the 1 in 23 or fewer in large population groups.

The reverse situation is to prevent genetic disease with controlled mating. In a program called Dor Yeshorim, for example, young people take tests for a dozen genetic disorders that are much more common among Jewish people of eastern European descent (Ashkenazim). Results are stored in a confidential database. Two people wishing to have children together can find out if they are carriers for the same disorder. If so, they may elect not to have children. Thousands of people have been

tested, and the program is partly responsible for the near-disappearance of Tay-Sachs disease among Ashkenazi Jews—although an episode of the television program "Law and Order" presents it as solely a Jewish disease.

A population that practices consanguinity has very nonrandom mating. Recall from chapter 4 that a consanguineous relationship is one in which "blood" relatives have children together. On the family level, this practice increases the likelihood that harmful recessive alleles from shared ancestors will be combined and passed to offspring, causing disease. The birth defect rate in offspring is 2.5 times the normal rate of about 3 percent. On a population level, consanguinity decreases genetic diversity. The

proportion of homozygotes rises as that of heterozygotes falls.

Some populations encourage marriage between cousins, which increases the incidence of certain recessive disorders. In certain parts of the middle east, Africa, and India, 20 to 50 percent of marriages are between cousins, or uncles and nieces. The tools of molecular genetics can reveal these relationships. Researchers traced DNA sequences on the Y chromosome and in mitochondria among residents of an ancient, geographically isolated “micropopulation” on the island of Sardinia, near Italy. They consulted archival records dating from the village’s founding by 200 settlers around 1000 A.D. to determine familial relationships. Between 1640 and 1870, the population doubled, reaching 1,200 by 1990. Fifty percent of the present population descends from just two paternal and four maternal lines, and 86 percent of the people have the same X chromosome. Researchers are analyzing disorders that are especially prevalent in this population, which include hypertension and a kidney disorder.

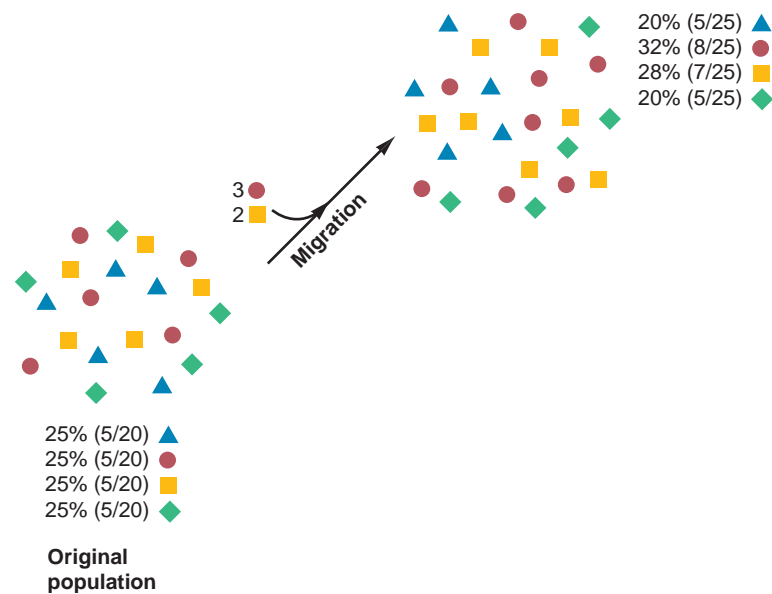
Worldwide, about 960 million married couples are related, and know of their relationship. Also contributing to nonrandom mating is endogamy, which is marriage within a community. In this case, spouses may be distantly related and unaware of the connection.

## Key Concepts

1. People choose mates for many reasons, and they do not contribute the same numbers of children to the next generation. These practices change allele frequencies in populations.
2. Traits lacking obvious phenotypes may be in Hardy-Weinberg equilibrium.
3. Consanguinity and endogamy increase the proportion of homozygotes in a population.

## 15.2 Migration

Large cities, with their pockets of ethnicity, defy Hardy-Weinberg equilibrium by their very existence. Waves of immigrants formed the population of New York City, for example. The original Dutch settlers of



**Figure 15.3 Migration alters allele frequencies.** If the population travels and picks up new individuals, allele (and genotype) frequencies can change.

the 1600s had different alleles than those in today’s metropolis of English, Irish, Slavics, Africans, Hispanics, Italians, Asians, and many others. **Figure 15.3** depicts the effect on allele and genotype frequencies when individuals join a migrating population. Clues to past migrations lie in historical documents as well as in differing allele frequencies in regions defined by geographical or language barriers.

The frequency of the allele that causes galactokinase deficiency (OMIM 230200) in several European populations reveals how people with this autosomal recessive disorder migrated (**figure 15.4**). Galactokinase deficiency causes cataracts (clouding of the lens) in infants. It is very common among a population of 800,000 gypsies, called the Vlach Roma, who live in Bulgaria. It affects 1 in 1,600 to 2,500 people among them, and 5 percent of the people are carriers. But among all gypsies in Bulgaria as a whole, the incidence drops to 1 in 52,000. As the map in figure 15.4 shows, the disease becomes rarer to the west. This pattern may have arisen when people with the allele settled in Bulgaria, with only a few individuals or families moving westward.

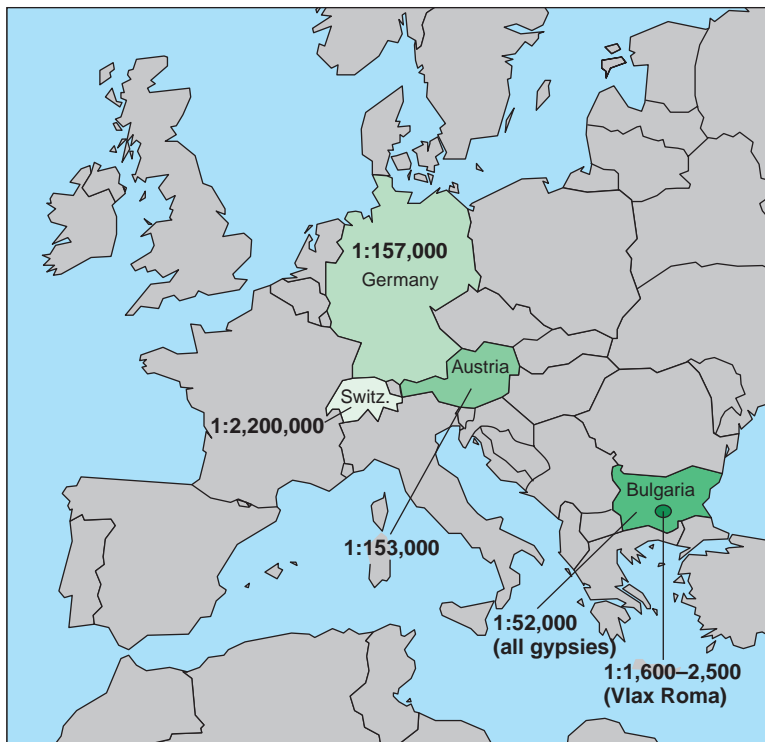
Allele frequencies often reflect who ruled whom. For example, the frequency of ABO blood types in certain parts of the world today mirrors past Arab rule. The distribution of ABO blood types is very similar in northern Africa, the Near East, and

southern Spain. These are precisely the regions where Arabs ruled until 1492. The uneven distribution of allele frequencies can also reveal when and where nomadic peoples stopped. For example, in the eighteenth century, European Caucasians called trekboers migrated to the Cape area of South Africa. The men stayed and had children with the native women of the Nama tribe. The mixed society remained fairly isolated, leading to the distinctive allele frequencies found in the present-day people of color of the area.

Sometimes allele frequencies change from one neighboring population to another. This phenomenon is termed a **cline**. Changing allele frequencies usually reflect migration patterns, as immigrants introduced alleles and emigrants removed them. Clines may be gradual, reflecting unencumbered migration paths, but barriers often cause more abrupt changes in allele frequencies. Geographical formations such as mountains and bodies of water may block migration, maintaining population differences in allele frequencies on either side of the barrier. Language differences may also isolate alleles, if people who cannot communicate tend not to have children together.

Allele frequencies up and down the lush strip of fertile land that hugs the Nile River illustrate the concept of clines. Researchers found a gradual change in mitochondrial





**Figure 15.4 Galactokinase deficiency in Europe illustrates a cline.** This autosomal recessive disorder that causes blindness varies in prevalence across Europe. It is most common among the Vlax Roma gypsies in Bulgaria. The condition becomes much rarer to the west, as indicated by the shading from dark to light green.

DNA sequences in 224 people who live on either side of the Nile, an area settled 15,000 years ago. The farther apart two individuals live along the Nile, the less alike their mtDNA. This is consistent with evidence from mummies and historical records that indicate the area was once kingdoms separated by wars and language differences. If the area had been one large interacting settlement, then the DNA sequences would have been more mixed. Instead, the Nile may have served as a “genetic corridor” between Egypt and sub-Saharan Africa.

Clines may also reflect human dependence on communication. Geneticists correlated twenty blood types to geographically defined regions of Italy and to areas where a single dialect is spoken. They chose Italy because it is rich in family history records and linguistic variants. Six of the blood types varied more consistently with linguistically defined subregions than with geographical regions. Perhaps differences in language prevent people from socializing, keeping alleles within groups.

## Key Concepts

1. Migration alters genotype frequencies by adding and removing alleles from populations.
2. Clines are gradual changes in allele frequencies between neighboring populations.
3. Geographical barriers and language differences often create great differences in allele frequencies.

## 15.3 Genetic Drift

When a small group separates from a larger population, or reproduce only among themselves, allele frequencies may change as a result of chance sampling from the whole (**figure 15.5**). This change in allele frequency that occurs when a small group separates from the larger whole is termed **genetic drift**. It is like reaching into a bag of jellybeans and, by chance, grabbing only green and yellow ones. The allele frequency changes in genetic drift are random and unpredictable, just as reaching into the jellybean bag a second time might yield mostly black and orange candies.

Genetic drift occurs when the population size plummets, due either to migration, to a natural disaster that isolates small pockets of people, or to the consequences of human behavior. Members of a small community might reproduce only among themselves, which keeps genetic variants within their ethnic group. Pittsburgh, Pennsylvania and New York City are more mosaics of groups with distinct ethnic flavors than “melting pots” of mixed heritage.

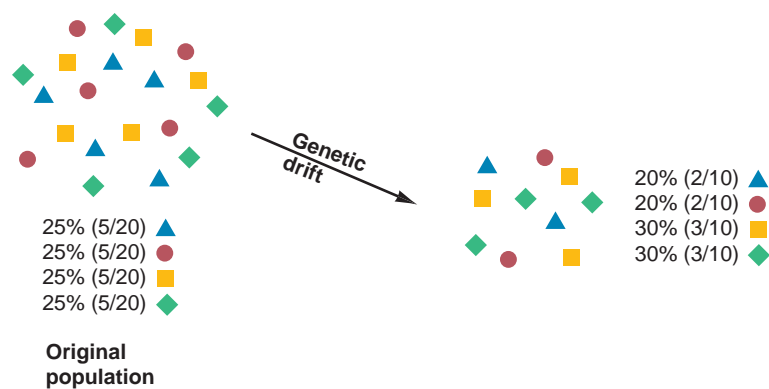
Some groups of people become isolated in several ways—geographically, linguistically, and by choice of partners. Such populations often have a high incidence of several otherwise rare inherited conditions. The native residents of the Basque country in the western part of the Pyrenees Mountains between France and Spain, for example, still speak remnants of Euskera, a language the first European settlers brought in more than 10,000 years ago. The Basques have unusual frequencies of certain ABO and Rh blood types, rare mtDNA sequences and cell surface antigen patterns, and a high incidence of a mild form of muscular dystrophy.

## The Founder Effect

A common type of genetic drift in human populations is the **founder effect**, which occurs when small groups leave home to found new settlements. The new colony may have different allele frequencies than the original population.

Founder populations can amplify certain alleles. This shows up in increased disease frequencies. Consider an isolated community of about 10,000 members of a religious sect who live on an isolated plateau on the Utah-Arizona border. Half of all known cases of fumarate deficiency (OMIM 606812), which causes mental retardation, seizures, and coma, occur in this area. Nearly 80 percent of the population descends from two original settlers, one of whom brought in the mutation. Widespread cousin-cousin marriages as well as polygamy (men with multiple wives) and social isolation have joined the powerful founder effect to keep the disease in the population. Although this founder effect is recent—since the 1930s—the extreme non-random mating and smallness of the founder group have sped the increase in the number of cases of this otherwise very rare disorder. **Table 15.1** lists some other founder populations.





**Figure 15.5 Genetic drift alters allele frequencies.** If members of a population leave or do not reproduce, allele frequencies can change by chance sampling of a small population. When half of this population does not contribute to the next generation, two genotypes increase in frequency and two decrease.

**Table 15.1**

### Founder Populations

Population	Number of Founders	Number of Generations	Population Size Today
Costa Rica	4,000	12	2,500,000
Finland	500	80–100	5,000,000
Hutterites	80	14	36,000
Japan	1,000	80–100	120,000,000
Iceland	25,000	40	300,000
Newfoundland	25,000	16	500,000
Quebec	2,500	12–16	6,000,000
Sardinia	500	400	1,660,000

A powerful founder effect appears in the French Canadian population of Quebec. Their lack of diversity in disease-causing mutations reflects a long history of isolation. Consider breast cancer caused by the *BRCA1* gene. More than 500 alleles are known worldwide, yet only four are seen among French Canadians. Several inborn errors of metabolism are also more common in this group. The French Canadians have ideal characteristics for gene discovery: many generations since founding (14), few founders (about 2,500), a high rate of population expansion (74 percent increase per generation), a large present-day population (about 6 million), and most marriages within the group.

The French Canadian population exemplifies genetic drift because the people have kept mostly to themselves within a larger population. The French founded Quebec City in 1608. Until 1660, the population grew as immigrants arrived from France,

and then began to increase from births. More than 10,000 French had arrived by the time the British took over in 1759, but many of them had headed westward, taking their genes with them. Meanwhile, in Quebec, religious, language, and other cultural differences separated the French and English gene pools. The French Canadian population of Quebec grew from the 2,500 or so founding genotypes to about 6 million individuals today.

The cultural and physical isolation in Canada created an unusual situation—a founder effect within a founder effect. In the nineteenth century, when agricultural lands opened up about 150 miles north of Quebec, some families migrated north. Their descendants, who remained in the remote area, form an incredibly genetically homogeneous subpopulation of founders split off from the original set of founders.

A classic example of a founder effect within a larger population is the Dunker

community of Germantown, Pennsylvania. Excellent historical records combined with distinctive traits enabled geneticists to track genetic drift from the larger surrounding population. The Dunkers came from Germany between 1719 and 1729, but they have lived among others since that time. Still, the frequencies of some genotypes are different among the Dunkers than among their non-Dunker neighbors, and they are also different from the frequencies seen among people living in their native German village. The Dunkers have a different distribution of blood types (**table 15.2**) and much higher incidence of attached earlobes, hyperextensible thumbs, hairs in the middle of their fingers, and left-handedness compared to the other two groups.

Founder effects can be studied at the phenotypic and genotypic levels. Phenotypically, a founder effect is indicated when a community of people, known from local history to have descended from a few founders, have inherited traits and illnesses that are rare elsewhere. This is striking among the Old Order Amish and Mennonites of Lancaster County, Pennsylvania. Often, worried parents would bring their ill children to medical facilities in Philadelphia. Over the years, researchers realized that these people are subject to an array of extremely rare conditions (**table 15.3** and **figure 15.6**). For example, Victor McKusick, founder of *Online Mendelian Inheritance in Man*, discovered and described cartilage-hair hypoplasia after six Amish children died at a Philadelphia hospital from chickenpox in 1965. Part of their inherited syndrome was impaired immunity, and the children succumbed to this usually mild illness. Until McKusick made the connection, the other symptoms—including dwarfism, sparse hair, and anemia—were not recognized as part of a syndrome. Today, as many geneticists study inherited diseases common among the Amish and Mennonites, treatments are becoming available, from special diets to counter inborn errors of metabolism to gene therapy.

In addition to historical records, differences in allele frequencies in a smaller population compared to those in the general population suggest a founder effect. The incidence of certain diseases in Lancaster County, for example, is astounding. Maple syrup urine disease affects 1 in 225,000

Table 15.2

## Genetic Drift and the Dunkers

Blood Type	U.S.	Population	
		Dunker	European
ABO System			
A	40%	60.0%	45%
B, AB	15%	5.0%	15%
Rh <sup>-</sup>	15%	11.0%	15%
MN System			
M	30%	44.5%	30%
MN	50%	42.0%	50%
N	20%	13.5%	20%

Table 15.3

## Inherited Conditions Common Among the Amish and Mennonites of Lancaster County, Pennsylvania

Disorder	OMIM	Signs and Symptoms (Phenotype)
Ataxia telangiectasia	208900	Increased sensitivity to radiation, loss of balance and coordination, red marks on face, delayed sexual maturation, lung infections, diabetes, high risk of cancer
Bipolar affective disorder	Several	Mood swings (manic depression)
Cartilage-hair hypoplasia (metaphyseal chondrodysplasia, McKusick type)	250250	Dwarfism, sparse hair, anemia, poor immunity
Crigler-Najjar syndrome	218800	Bilirubin buildup, jaundice, brain damage
Ellis-van Creveld syndrome	225500	Dwarfism, short fingers, underdeveloped nails, polydactyly, hair “blaze” pattern, heart disease, fused bones, teeth at birth
Glutaric aciduria type I	231670	Paralysis, brain damage
Homocystinuria	236200	Damaged blood vessels, stroke, heart attack
Limb-girdle muscular dystrophy	253600	Progressive muscle weakness in limbs
Maple syrup urine disease	248600	Sweet-smelling urine, sleepiness, vomiting, mental retardation
Metachromatic leukodystrophy	250100	Rigid muscles, convulsions, mental deterioration
Morquio syndrome	252300	Clouded corneas, abnormal skeleton and aortic valve
Sudden infant death syndrome with dysgenesis of testes	608800	Sudden cessation of heartbeat and breathing; underdeveloped testes

newborns in the United States, but 1 in 400 newborns among the Lancaster families! A research fellow at Children’s Hospital in Philadelphia discovered that cerebral palsy in several young children from Lancaster County attributed to oxygen deprivation

at birth was actually an inborn error of metabolism called glutaric aciduria type I. He went from farm to farm, tracking cases against genealogical records, and found that *every family* that could trace its roots back to the founders had members who had the



**Figure 15.6 Ellis-van Creveld syndrome.** This Amish child has Ellis-van Creveld syndrome. He has short-limbed dwarfism, extra fingers, heart disease, fused wrist bones, and had teeth at birth. The condition is autosomal recessive, and the mutant allele is in 7 percent of the people of this community. Affected individuals have severe dwarfism, but heterozygotes have the milder condition Weyers acrocentric dysostosis. These were thought to be different disorders until the gene was discovered.

disease! Today, 0.5 percent of newborns in this population have the condition.

A mutation that is the same in all affected individuals in a population is strong evidence of a founder effect due to descent from shared ancestors. The Bulgarian gypsies who have galactokinase deficiency, for example, all have a mutation that is extremely rare elsewhere. In contrast, a population with several mutations that cause the same disorder is more likely to have picked up those variants from people joining the group, rather than from descent from shared founders.

Very often when a disease-associated allele is identical in DNA sequence among people in the same population, so is the DNA surrounding the gene. This pattern indicates that a portion of a chromosome, rather than just the disease-causing gene, has been passed among the members of the

population from its founders. For this reason, many studies that trace founder effects examine haplotypes that include tightly linked genes.

When historical or genealogical records are particularly well kept or recent, founder effects can sometimes be traced to the very beginning. This is the case for the Afrikaner population of South Africa. The 2.5 million Afrikaners descended from a small group of Dutch, French, and German immigrants who had huge families, often with as many as ten children. In the nineteenth century, some Afrikaners migrated northeast to the Transvaal Province, where they lived in isolation until the Boer War in 1902 introduced better transportation.

Today, 30,000 Afrikaners have porphyria variegata (see figures 5.5 and 5.6). All affected people descended from one couple who came from the Netherlands in 1688! Today's allele frequency in South Africa is far higher than that in the Netherlands because the founding couple had many children—who, in turn, had large families, passing on and amplifying the dominant mutation.

Founder effects are also evident in more common illnesses, where populations have different mutations in the same gene. *BRCA1* breast cancer, for example, is most prevalent among Ashkenazi Jewish people. Nearly all affected individuals have the same 3-base deletion. In contrast, *BRCA1* breast cancer is rare in blacks, but it affects families from the Ivory Coast in Africa, the Bahamas, and the southeastern United States. They share a 10-base deletion, probably inherited from West Africans ancestral to all three modern groups. Slaves brought the disease to the United States and the Bahamas between 1619 and 1808, but some of their relatives who stayed in Africa have perpetuated the mutant allele here.

## Population Bottlenecks

A **population bottleneck** occurs when many members of a group die, and only a few are left to replenish the numbers. The new population has only those alleles in the small group that survived the catastrophe. An allele in the remnant population might become more common in the replenished population than it was in the original larger group. Therefore, the new population has

a much more restricted gene pool than the larger ancestral population, with some variants amplified, others diminished.

Population bottlenecks can occur when people (or other animals) colonize islands. An extreme example is seen among the Pingelapese people of the eastern Caroline islands in Micronesia. Four to 10 percent are born with “Pingelapese blindness,” an autosomal recessive combination of color-blindness, nearsightedness, and cataracts also called achromatopsia (OMIM 603096). Elsewhere, only 1 in 20,000 to 50,000 people inherits the condition. Nearly 30 percent of the Pingelapese are carriers. The prevalence of the blindness among the Pingelapese stems from a typhoon in 1780 that killed all but 9 males and 10 females who founded the present population. This severe population bottleneck, plus geographic and cultural isolation, increased the frequency of the blindness gene as the population resurged.

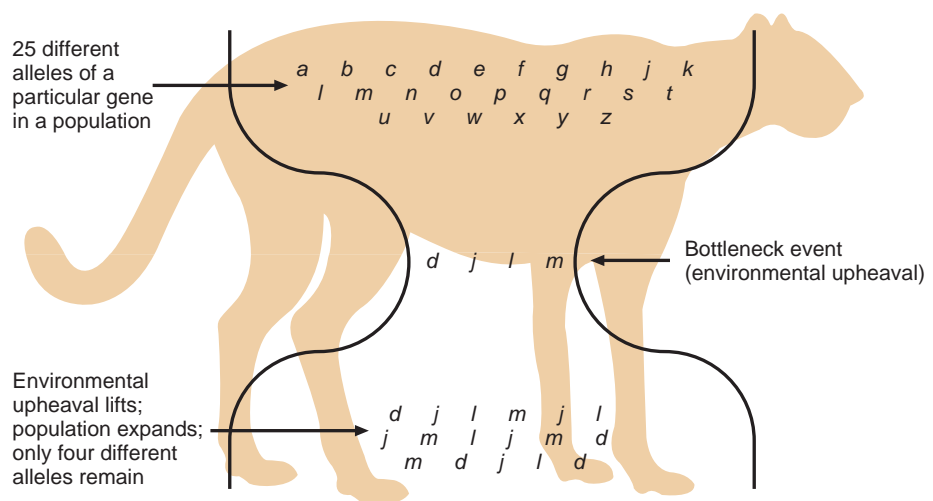
**Figure 15.7** illustrates schematically the dwindling genetic diversity that results from a population bottleneck. Today's cheetahs live in just two isolated populations of a few thousand animals in South and East Africa. Their numbers once exceeded 10,000. The South African cheetahs are so alike genetically that even unrelated animals can accept skin grafts from each other. Researchers attribute the cheetahs' genetic uniformity to two bottlenecks—one that occurred at

the end of the most recent ice age, when habitats changed, and another following mass slaughter by humans in the nineteenth century. However, the good health of the animals today indicates that the genes that have survived enable the cheetahs to thrive in their environment.

Human-wrought disasters that kill many people can also cause population bottlenecks—perhaps even more severely, because aggression is typically directed at particular groups, while a typhoon indiscriminately kills anyone in its path. The Chmielnicki massacre was one of many attacks against the Ashkenazim. Overall, these acts have left a legacy of several inherited diseases that are at least ten times more common among Jewish people than in other populations (**table 15.4**), although some of the disorders have become rarer as genetic testing has become available.

The Chmielnicki massacre began in 1648, when a Ukrainian named Bogdan Chmielnicki led a massacre against the Polish people, including peasants, nobility, and the Jewish people, in retaliation for a Polish nobleman's seizure of his possessions. By 1654, Russians, Tartars, Swedes, and others joined the Ukrainians in wave after wave of violence against the Polish people. Thousands perished, with only a few thousand Jewish people remaining.

The Jewish people have survived many massacres, and therefore many population



**Figure 15.7 Population bottlenecks.** A population bottleneck occurs when the size of a genetically diverse population drastically falls, remains at this level for a time, and then expands again. The new population loses some genetic diversity if alleles are lost. Cheetahs are difficult to breed in zoos because sperm quality is poor and many newborns die—both outcomes due to lack of genetic diversity.



Table 15.4

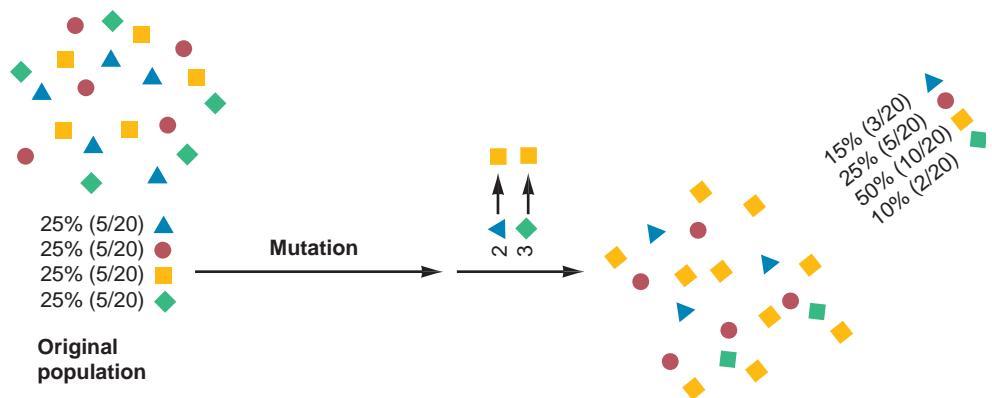
## Autosomal Recessive Genetic Diseases Prevalent Among Ashkenazi Jewish Populations

Disorder	OMIM	Signs and Symptoms (Phenotype)	Carrier Frequency
Bloom syndrome	210900	Sun sensitivity, short stature, poor immunity, impaired fertility, increased cancer risk	1/110
Breast cancer	113705, 600185	Malignant breast tumor caused by mutant <i>BRCA1</i> or <i>BRCA2</i> genes	3/100
Canavan disease	271900	Brain degeneration, seizures, developmental delay, death by 18 months of age	1/40
Familial dysautonomia	223900	No tears, cold hands and feet, skin blotching, drooling, difficulty swallowing, excess sweating	1/32
Gaucher disease	231000	Enlarged liver and spleen, bone degeneration, nervous system impairment	1/12
Niemann-Pick disease type A	257200	Lipid accumulation in cells, particularly in the brain; mental and physical retardation, death by age three	1/90
Tay-Sachs disease	272800	Brain degeneration causing developmental retardation, paralysis, blindness, death by age four	1/26
Fanconi anemia type C	227650	Deficiencies of all blood cell types, poor growth, increased cancer risk	1/89

bottlenecks; after the Chmielnicki massacre, like the others, their numbers grew again. From 1800 to 1939, the Jewish population in Eastern Europe swelled to several million. Yet massacres continued. Jewish people also tended to have children only with each other. Both of these factors—nonrandom mating and population bottlenecks—changed allele frequencies and contributed to the high incidence of certain inherited diseases seen among the Ashkenazim today. Several genetic testing companies offer “Jewish genetic disease” panels that are not meant to discriminate or stereotype, but are based on a genetic fact of life—some illnesses are more common in certain populations.

## Key Concepts

1. Genetic drift occurs when a subset of a population has different allele frequencies than the larger population.
2. The founder effect occurs when a few individuals leave a community to start a new settlement. The resulting population may, by chance, either lack some alleles from the original population or have high frequencies of others.
3. In a population bottleneck, many members die, and only a few contribute to the next generation.



**Figure 15.8 Mutation alters allele frequencies.** If one allele changes into another from one generation to the next, genotype frequencies can change.

## 15.4 Mutation

A major and continual source of genetic variation is mutation—when one allele changes into another (**figure 15.8**). Genetic variability also arises from crossing over and independent assortment during meiosis, but these events recombine existing traits rather than introduce new ones.

If a DNA base change occurs in a part of a gene that encodes part of a protein necessary for its function, then an altered trait may result. If a mutation occurs in a gamete, then the change can pass to future generations and affect an allele's frequency in the population.

Natural selection, discussed in the next section, eliminates alleles that adversely

affect reproduction. Yet harmful recessive alleles are maintained in heterozygotes and are reintroduced by new mutation. Therefore, all populations have some alleles that would be harmful if homozygous. The collection of such deleterious alleles in a population is called its **genetic load**.

The contribution that mutation makes to counter Hardy-Weinberg equilibrium is quite small compared to the influence of migration and nonrandom mating. Natural selection has the greatest influence. The spontaneous mutation rate is only about 30 bases per haploid genome in each gamete. Each of us probably has 5 to 10 recessive lethal alleles, most of which are “silent” due to the

degeneracy of the genetic code and changes that do not alter protein function.

## Key Concepts

1. Mutation alters genotype frequencies by introducing new alleles.
2. Heterozygotes and mutations maintain the frequencies of deleterious alleles in populations.

## 15.5 Natural Selection

Environmental change can alter allele frequencies when individuals with certain phenotypes are more likely to survive and reproduce than others. This differential survival to reproduce guided by environmental change is **natural selection** (figure 15.9). The chapter opener chronicles natural selection acting on the gene variant that enables people to digest lactose.

In natural selection, reproductive success is all-important, for this is what transmits favorable alleles and weeds out the unfavorable ones, ultimately impacting population structure and therefore microevolution. In the common phrase used synonymously with natural selection—“survival of the fittest”—“fit” actually refers to reproductive success, not to physical prowess or intelligence (unless those traits lead directly to

reproductive success). In a Darwinian sense, an unattractive and out-of-shape parent of ten is more “fit” than a gorgeous triathlete with one child.

Natural selection can retain an advantageous trait or banish one that has become dangerous in the prevailing environment. Retaining a trait is termed positive natural selection, and getting rid of a trait negative natural selection, but the “positive” and “negative” are not value judgments—they merely refer to staying or leaving. In Darwin’s time natural selection was thought to be primarily negative, but the ability to sequence genes has enabled us to actually measure and track the instances of positive selection that have sculpted our differences from our closest primate relatives.

Subtle nuances in DNA sequence provide a signature of sorts for positive selection. Specifically, a sign of positive selection is a gene in humans that has a counterpart in other primates, but in humans has at least one distinctive difference in the amino acid sequence. A change in the DNA sequence that does *not* substitute an amino acid does not change the protein, and therefore has no effect on the phenotype. Such a change therefore cannot be subject to natural selection.

Another sign of positive selection is a gene that varies little, if at all, from person to person. Positive selection is, in a sense, an evolutionary version of “if it ain’t broke, don’t fix it.” Reading 16.1 offers several

examples of traits that were positively selected in human evolution (tool use, walking and running upright, a large brain, speech), and at least one that was negatively selected (smelling acuity).

Natural selection acts on preexisting genetic variants and is uncontrolled and largely unpredictable. In contrast, artificial selection is controlled breeding with the intent of perpetuating individuals with a particular phenotype, such as a crop plant or fancy pet. Darwin’s idea of natural selection actually grew from his

observations of artificial selection of pigeons.

Our pets are products of intense artificial selection. The ancestral dog was probably similar to the modern wild dog of Australia,



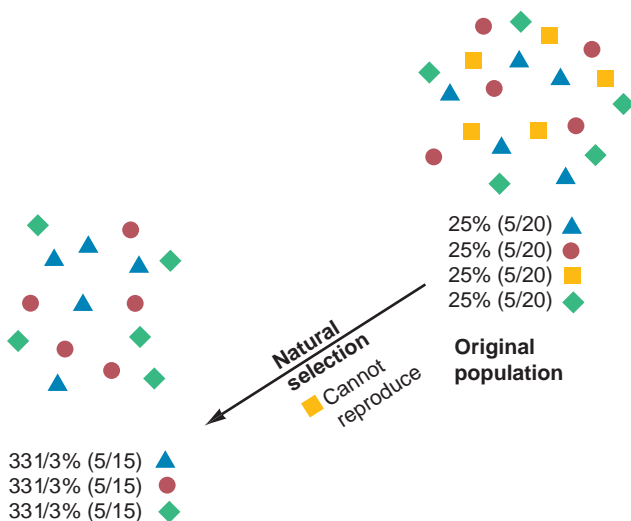
**Figure 15.10** Many of our pets reflect artificial selection. The American curl cat’s origin traces back to a stray female who wandered into the home of a cat-loving family in Lakewood, California, in 1981 and passed her unusual, curled-up ears to future generations. A dominant mutation leads to formation of extra cartilage lining the outer ear.

the dingo. It was introduced from southeast Asia in a tiny founder population about 5,000 years ago. From those ancestors, people bred the diverse dog breeds of today which, thanks to extreme artificial selection, suffer from more than 300 inherited disorders. Would natural selection have led to the basset hound with its painful back, the Pekingese with its unstable eyeballs, or the bulldog with its dental woes and notorious dog breath? Thanks to extreme artificial selection, today’s pure-bred dogs suffer from more than 300 inherited disorders. Cats were first domesticated in the Near East when agriculture began, about 10,000 years ago. They descended from one of five subspecies of wildcats (figure 15.10).

Natural selection can be seen in the appearance or reemergence of infectious diseases. If infection kills before reproductive age or impairs fertility, its spread will ultimately remove from the population individuals susceptible to infection. Disease incidence falls as only survivors are left. But if conditions change, the disease may resurge. This has happened with tuberculosis (TB).

## Tuberculosis Ups and Downs—and Ups

When TB first appeared in the Plains Indians of the Qu’Appelle Valley Reservation in Saskatchewan, Canada in the mid-1880s, it struck swiftly and lethally, infecting many



**Figure 15.9** Natural selection alters allele frequencies. If health conditions impair the ability of individuals of a certain genotype to reproduce, allele frequencies can change.



## Reading 15.1

# Antibiotic Resistance: The Rise of MRSA

Many antibiotic drugs are no longer effective. The reason is the interplay between mutation and natural selection.

Our bodies harbor populations of bacteria that have their own genetic variants, some of which enable the microorganism to survive in the presence of a particular antibiotic drug. When a sick person takes the drug, symptoms abate as sensitive bacteria die. The resistant mutants reproduce, taking over the niche the antibiotic-sensitive bacteria vacated. Soon, the person has enough antibiotic-resistant bacteria to feel ill again.

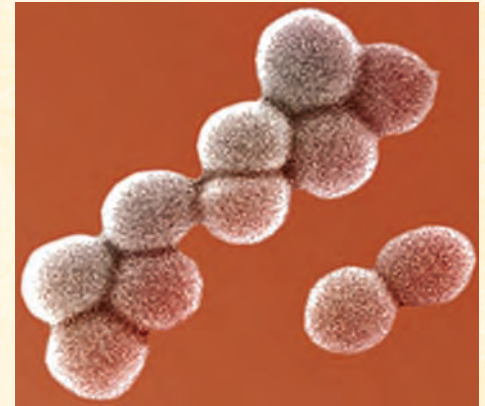
Usually antibiotic resistance genes already exist in the bacterial populations, and exposure to the drug selects the resistant bacteria. However, some antibiotics actually induce mutation. Resistant bacteria circumvent antibiotic actions in several ways. Penicillin kills bacteria by tearing apart their cell walls. Resistant microbes produce enzyme variants that dismantle penicillin, or have altered cell walls that the drug cannot bind. Erythromycin, streptomycin, tetracycline, and gentamicin kill bacteria by attacking their ribosomes, which are different from ribosomes in a human. Drug-resistant bacteria have altered ribosomes that the drugs cannot bind.

Bacteria become resistant in two ways. Their DNA can mutate, passing the resistance from one bacterial generation to the next by cell division. Or groups of resistance

genes are passed on transposons, which move from cell to cell as part of DNA circles called plasmids. Bacteria usually pass transposons to similar bacteria, but in the unnatural environment of a hospital, genes may flit to any bacterium, and drug resistances are passed quickly. This is what has happened with infection by the bacterium *Staphylococcus aureus*.

*S. aureus* is normally present in low numbers in the nose and on the skin, but in high numbers it causes pimples and boils, food poisoning, toxic shock syndrome, pneumonia, and surgical wound infections (figure 1). *S. aureus* infection is particularly dangerous in hospitals, spreading rapidly among people unable to fight it. This common bacterium became resistant to penicillin soon after the drug was introduced in the 1940s. A related penicillin, methicillin, worked for a time, but resistant bacterial strains appeared suddenly in 2000, at such an alarming rate that the microorganism has its own acronym: MRSA, for methicillin-resistant *Staph aureus*. Doctors have turned to another antibiotic, vancomycin, to treat MRSA, but the effort may be too late.

DNA sequencing revealed that in one hospital, *S. aureus* picked up vancomycin resistance from another type of bacterium. A foot ulcer in a dialysis patient in Detroit harbored vancomycin-resistant *Enterococcus faecalis* as well as two types of *S. aureus*, one resistant to the antibiotic and one sensitive.



**Figure 1 Antibiotic resistance.** These *staphylococcus aureus* bacteria are resistant to methicillin and several other antibiotics.

By sequencing the plasmids that included the resistance gene, investigators deduced that *S. aureus* picked up an *E. faecalis* plasmid bearing a vancomycin resistance gene called *vanA*. Then the *vanA* gene jumped to an *S. aureus* plasmid. Since then, similar scenarios of drug resistance gene sharing among microorganisms have happened in many countries.

The frightening part of the rise of MSRA infection relates back to natural selection, which in this case benefits the pathogen, and not us. That is, bacteria that can resist the drugs that we use to fight them will survive and reproduce, ensuring that *Staphylococcus aureus* infection continues.

organs. Ten percent of the population died. But by 1921, TB tended to affect only the lungs, and only 7 percent of the population died annually from it. By 1950, mortality was down to 0.2 percent.

Outbreaks of TB ran similar courses in other human populations. The disease appeared in crowded settlements where the bacteria easily spread in exhaled droplets. In the 1700s, TB raged through the cities of Europe. Immigrants brought it to the United States in the early 1800s, where it also swept the cities. But TB incidence and virulence fell dramatically in the cities of

the industrialized world in the first half of the twentieth century—before antibiotic drugs were discovered. What tamed tuberculosis?

Natural selection, operating on both the bacterial and human populations, lessened the virulence of the infection. Some people inherited resistance and passed this beneficial trait on. At the same time, the most virulent bacteria killed their hosts so quickly that the victims had no time to spread the infection. As the deadliest bacteria were selected out of the population (negative selection), and as people who inherited

resistance mutations contributed more to the next generation (positive selection), TB gradually evolved from a severe, acute, systemic infection to a rare chronic lung infection. This was true until the late 1980s, when shifting events created conditions ideal for the infection's return. At first, complacency was responsible for the resurgence of TB infection that caused disease (some people are symptomless carriers). Funding for TB research dried up because the infection was considered "cured." Patients thought themselves cured when antibiotics treated the symptoms in a few months, abandoning the



drugs yet unknowingly continuing to spread the bacteria. Treatment in the 1950s— isolating patients for 18 months or longer in facilities called sanatoria—was actually more effective by quarantining infectious individuals. Then AIDS happened.

AIDS shattered immunity, providing millions of vulnerable human lungs to support TB bacteria—which had never vanished, just retreated into milder forms. With so many more lungs to infect, bacterial mutations began to accumulate, and variants resistant to antibiotic drugs arose. Today, one-third of the 40 million HIV-infected people worldwide also have TB. Someone with HIV faces a fifty-fold increased risk of contracting TB. Each disease speeds the course of the other. In terms of public health, the most frightening aspect of the problem of dual infection is that a person with HIV can pass TB to anyone in just a sneeze or cough.

Further evidence of evolution is that the bacteria that cause TB are becoming resistant to many types of antibiotic drugs. Resistance genes are passed on genetic elements called transposons (discussed in section 11.4), which means that a bacterium can pick up several resistances at once. Today, multidrug-resistant TB accounts for about 10 percent of cases in many nations, and up to 50 percent of cases in China, Russia, and India. In these three nations, poverty and faltering health care systems have introduced the stress and malnutrition that impair immunity, which allows TB to take hold. Symptoms are bloody cough, weight loss, lack of appetite, fever, and night sweats.

The HIV epidemic and stressful environments such as prisons and orphanages in Russia continue to provide breeding grounds for TB, but the problem may be coming under control, thanks to a program from the World Bank, World Health Organization, and the Global Fund. The program is introducing earlier diagnosis and treatment, monitoring of antibiotic treatment for six to eight months, and improved reporting and surveillance of cases. However, the resurgence of TB should remind us never to underestimate the evolution that operates in all organisms—and does so unpredictably. Reading 15.1 discusses antibiotic resistance.

## Evolving HIV

Because the RNA or DNA of viruses replicates often and errors are not repaired, viral mutations accumulate rapidly. Like bacteria, the viruses in a human body form a population, including naturally occurring genetic variants. In HIV infection, natural selection controls the diversity of HIV genetic variants within a human body as the disease progresses. The human immune system and drugs to slow the infection become the environmental factors that select (favor) resistant viral variants.

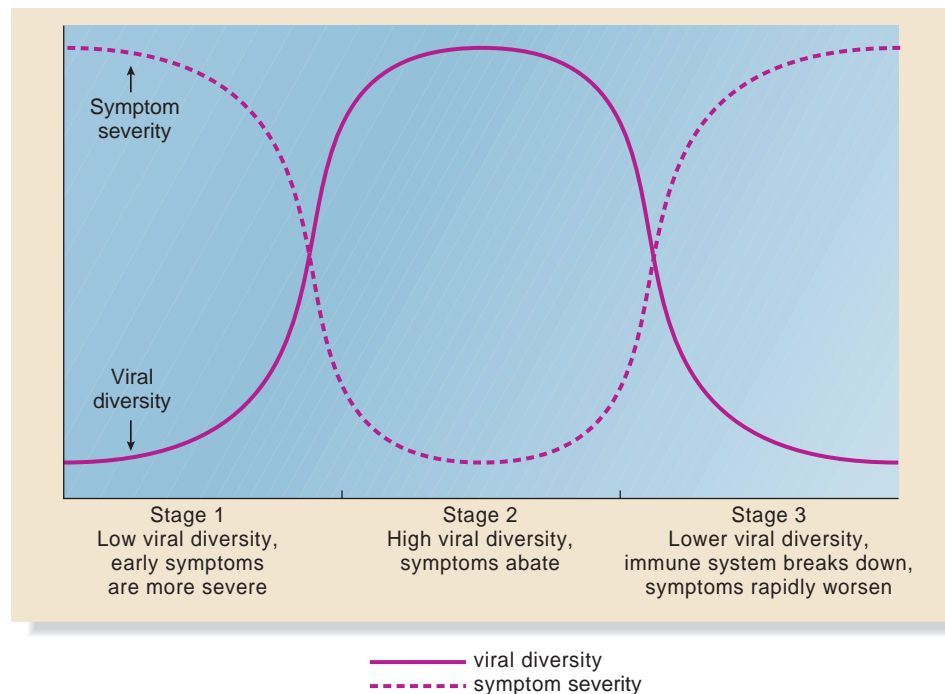
HIV infection can be divided into three stages, both from the human and the viral perspective (**figure 15.11**). A person infected with HIV may experience an initial acute phase, with symptoms of fever, night sweats, rash, and swollen glands. In a second period, lasting from 2 to 15 years, health usually returns. In a third stage, immunity collapses, the virus replicates explosively, and opportunistic infections and cancer eventually cause death.

The HIV population changes and expands throughout the course of infec-

tion, even when the patient seems to stay the same for a long time. New mutants continuously arise, and they alter such traits as speed of replication and the patterns of molecules on the viral surface.

In the first stage of HIV infection, as the person battles acute symptoms, viral variants that replicate swiftly predominate. In the second stage, the immune system starts to fight back and symptoms abate, as viral replication slows and many viruses are destroyed. Now natural selection acts, and certain viral variants reproduce and mutate, giving rise to a diverse viral population. Ironically, drugs used to treat AIDS may further select against the weakest HIV variants. Gradually, the HIV population overtakes the immune system cells, but years may pass before immunity begins to noticeably decline. The third stage, full-blown AIDS, occurs when the virus overwhelms the immune system. With the selective pressure off, viral diversity again diminishes, and the fastest-replicating variants predominate. HIV wins.

The entire scenario of HIV infection reflects the value of genetic diversity—to



**Figure 15.11 Natural selection of HIV** Natural selection controls the genetic diversity of an HIV population in a person's body. Before the immune system gathers strength, and after it breaks down, HIV diversity is low. A rapidly reproducing viral strain predominates, although new mutations continually arise. During the 2- to 15-year latency period, viral variants that can evade the immune system gradually accumulate.

enable the survival of a population or species in the face of an environmental threat. When that threat—an immune system attack or drugs—wipes out sensitive variants, one genotype may prevail.

Knowing that HIV diversifies early in the course of infection has yielded clinical benefits. This is why patients now take combinations of drugs right after diagnosis. The drugs act in different ways to squelch several viral variants simultaneously, slowing the course of the infection. For many people, thanks to declining viral genetic diversity, HIV infection has become a chronic illness rather than the swift killer that it was when the epidemic began.

### Balanced Polymorphism

If natural selection eliminates individuals with detrimental phenotypes from a population, then how do harmful mutant alleles remain in a gene pool? Harmful recessive alleles are replaced in two ways: by new mutation, and by persistence in heterozygotes.

Sometimes, a recessive condition remains particularly prevalent because the heterozygote enjoys some unrelated health advantage, such as being resistant to an infectious disease or able to survive an environmental threat. This “heterozygous advantage”

that maintains a recessive, disease-causing allele in a population is called **balanced polymorphism**. Recall that *polymorphism* means variant; the effect is *balanced* because the protective effect of the noninherited condition counters the negative effect of the deleterious allele, maintaining its frequency in the population. Balanced polymorphism is a type of balancing selection, which more generally refers to maintaining heterozygotes in a population. A few examples follow, and these and others are summarized in **table 15.5**.

### Sickle Cell Disease and Malaria

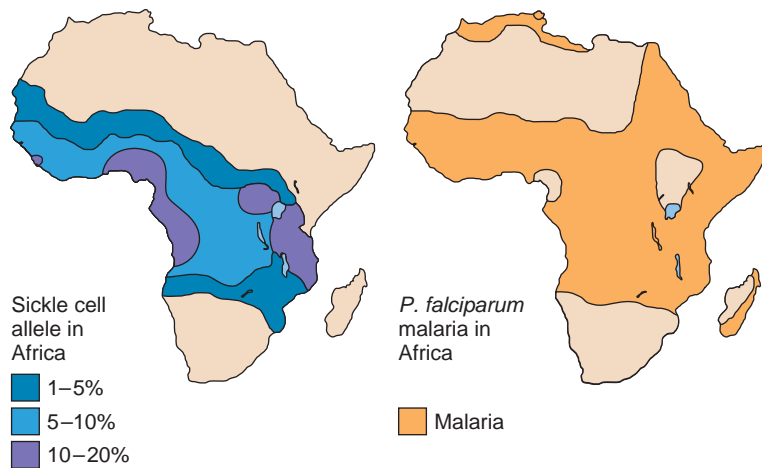
Sickle cell disease is an autosomal recessive disorder that causes anemia, joint pain, a swollen spleen, and frequent, severe infections (see the opener to chapter 12). It is the classic example of balanced polymorphism: carriers are resistant to malaria, or develop very mild cases. Malaria is an infection by the parasite *Plasmodium falciparum* and related species that causes debilitating cycles of chills and fever. The parasite spends the first stage of its life cycle in the salivary glands of the mosquito *Anopheles gambiae*. When an infected female mosquito draws blood from a human, malaria parasites enter red blood cells, which transport the parasites to the liver. The red blood cells burst, releasing parasites throughout the body.

In sickle cell disease, many red blood cells burst prematurely, which expels the parasites before they can cause rampant infection. The blood of a person with sickle cell disease is also thicker than normal, which may hamper the parasite’s ability to infect. A sickle cell disease carrier’s blood is abnormal enough to be inhospitable to the malaria parasite—but usually not abnormal enough to cause the blocked circulation of sickle cell disease.

A clue to the protective effect of being a carrier for sickle cell disease came from striking differences in the incidence of the two diseases in different parts of the world (**figure 15.12**). In the United States, 8 percent of African Americans are sickle cell carriers, whereas in parts of Africa, up to 45 to 50 percent are carriers. Although Africans had known about a painful disease that shortened life, the sickled cells weren’t recognized until 1910 (see section 12.1). In 1949, British geneticist Anthony Allison found that the frequency of sickle cell carriers in tropical Africa was higher in regions where malaria rages all year long. Blood tests from children hospitalized with malaria showed that nearly all were homozygous for the wild type sickle cell allele. The few sickle cell carriers among them had the mildest cases of malaria. Was malaria enabling the sickle cell allele to persist by felling people

**Table 15.5**  
Balanced Polymorphism

Disease 1 (inherited, carrier)	Protects against →	Disease 2	Because →	Mechanism	References
Sickle cell disease		Malaria		Abnormal red blood cells cannot retain parasites	Section 12.1
G6PD deficiency		Malaria		Parasite cannot reproduce in abnormal red blood cells	Section 12.5
PKU		Fungal infection in fetuses		Elevated phenylalanine inactivates fungal toxin	Sections 5.1, 14.1, 15.6
Prion protein mutation		Transmissible spongiform encephalopathy		Prion protein cannot misfold in presence of infectious prion protein	Figure 10.20 Section 12.4 Reading 10.1
CF		Diarrheal disease (cholera, typhus)		Fewer chloride channels in intestinal cells prevent water loss	Sections 14.1, 14.3 Reading 2.2
Smith-Lemli-Opitz syndrome		Cardiovascular disease		Lowered serum cholesterol	OMIM 270400 (multiple birth defects, mental retardation)



**Figure 15.12 Balanced polymorphism.** Comparing the distribution of people with malaria and people with sickle cell disease in Africa reveals balanced polymorphism. Carriers for sickle cell disease are resistant to malaria because changes in the blood caused by the sickle cell allele are not severe enough to impair health, but they do inhibit the malaria parasite.

who did not inherit it? The fact that sickle cell disease is rarer where malaria is rare supports the idea that sickle cell heterozygosity protects against the infection.

Further evidence of a sickle cell carrier's advantage in a malaria-ridden environment is the fact that the rise of sickle cell disease parallels the cultivation of crops that provide breeding grounds for *Anopheles* mosquitoes. About 1000 B.C., Malayo-Polynesian sailors from southeast Asia traveled in canoes to East Africa, bringing new crops of bananas, yams, taros, and coconuts. When the jungle was cleared to grow these crops, the open space provided breeding grounds for the mosquitoes. The insects, in turn, offered a habitat for part of the life cycle of the malaria parasite.

The sickle cell allele may have been brought to Africa by people migrating from Southern Arabia and India, or it may have arisen directly by mutation in East Africa. However it happened, people who inherited one copy of the sickle cell allele survived or never contracted malaria—the essence of natural selection. These carriers had more children and passed the protective allele to approximately half of them. Gradually, the frequency of the sickle cell allele in East Africa rose from 0.1 percent to 45 percent in 35 generations. Carriers paid the price for this genetic protection, however, whenever two of them produced a child with sickle cell disease.

A cycle set in. Settlements with large numbers of sickle cell carriers escaped debilitating

malaria. They were strong enough to clear even more land to grow food—and support the disease-bearing mosquitoes.

### Prion Disease and Cannibalism

Being a heterozygote for the prion protein gene may protect against the disorders of protein folding called transmissible spongiform encephalopathies (see figure 10.20, Reading 10.1, and section 12.4). The best studied such illness is kuru, which caused brain degeneration among the Foré people in Papua New Guinea until the Australian government halted the practice of ritual cannibalism in the mid-1950s. A recent investigation of the prion protein gene among 30 elderly Foré women who had eaten brains revealed 23 heterozygotes. Only 15 were predicted based on Hardy-Weinberg equilibrium observed among 140 Foré who had not eaten brains. In the heterozygotes, some of the normal prion proteins have a valine at amino acid position 129, and some a methionine. The different amino acids somehow prevent infectious misfolding in the presence of abnormal prion protein—as happens in cannibalism. All of the people in the United Kingdom who have developed variant CJD, the human form of “mad cow disease,” have only methionine at position 129.

The overrepresentation of heterozygotes among the Foré survivors led to the hypothesis that balancing selection has favored this

genotype in the population, and that cannibalism may have been the driving force. That is, homozygotes who were cannibals died of a prion disorder before reproducing, leaving the resistant heterozygotes to slowly accumulate in the population.

This new genetic view of cannibalism supports anthropological evidence that eating human flesh has occurred in many times and places, from Neanderthal caves in France and Croatia to the American Southwest. Evidence of cannibalism includes human bones damaged in ways similar to the bones of animals prepared for consumption, such as scratch marks to remove muscle and signs of breaking and crushing to obtain marrow. Biochemical evidence for past cannibalism includes human myoglobin, found only in human muscle, in fossilized human excrement.

### Cystic Fibrosis and Diarrheal Disease

Balanced polymorphism may explain why CF is so common—its cellular defect protects against diarrheal illnesses such as cholera and typhus. Diarrheal disease epidemics have left their mark on many human populations, and continue to be a major killer in the developing world.

Severe diarrhea rapidly dehydrates the body and leads to shock, kidney and heart failure, and death in days. In cholera, bacteria produce a toxin that opens chloride channels in cells of the small intestine. As salt (NaCl) leaves the intestinal cells, water rushes out, producing diarrhea. Cholera opens chloride channels, releasing chloride and water. The CFTR protein does just the opposite, closing chloride channels and trapping salt and water in cells, which dries out mucus and other secretions. A person with CF is very unlikely to contract cholera, because the toxin cannot open the chloride channels in the small intestine cells.

CF carriers enjoy the mixed blessing of balanced polymorphism. They do not have enough abnormal chloride channels to cause the labored breathing and clogged pancreas of cystic fibrosis, but they do have enough of a defect to prevent the cholera toxin from taking hold. During the devastating cholera epidemics that have occurred throughout history, individuals carrying mutant CF alleles had a selective advantage,



and they disproportionately transmitted those alleles to future generations.

However, because CF arose in western Europe and cholera originated in Africa, an initial increase in CF heterozygosity may have been a response to a different diarrheal infection—typhoid fever. The causative bacterium, *Salmonella typhi*, rather than producing a toxin, enters cells lining the small intestine—but only if CFTR channels are present. The cells of people with severe CF manufacture CFTR proteins that never reach the cell surface, and therefore no bacteria get in. Cells of CF carriers admit some bacteria.

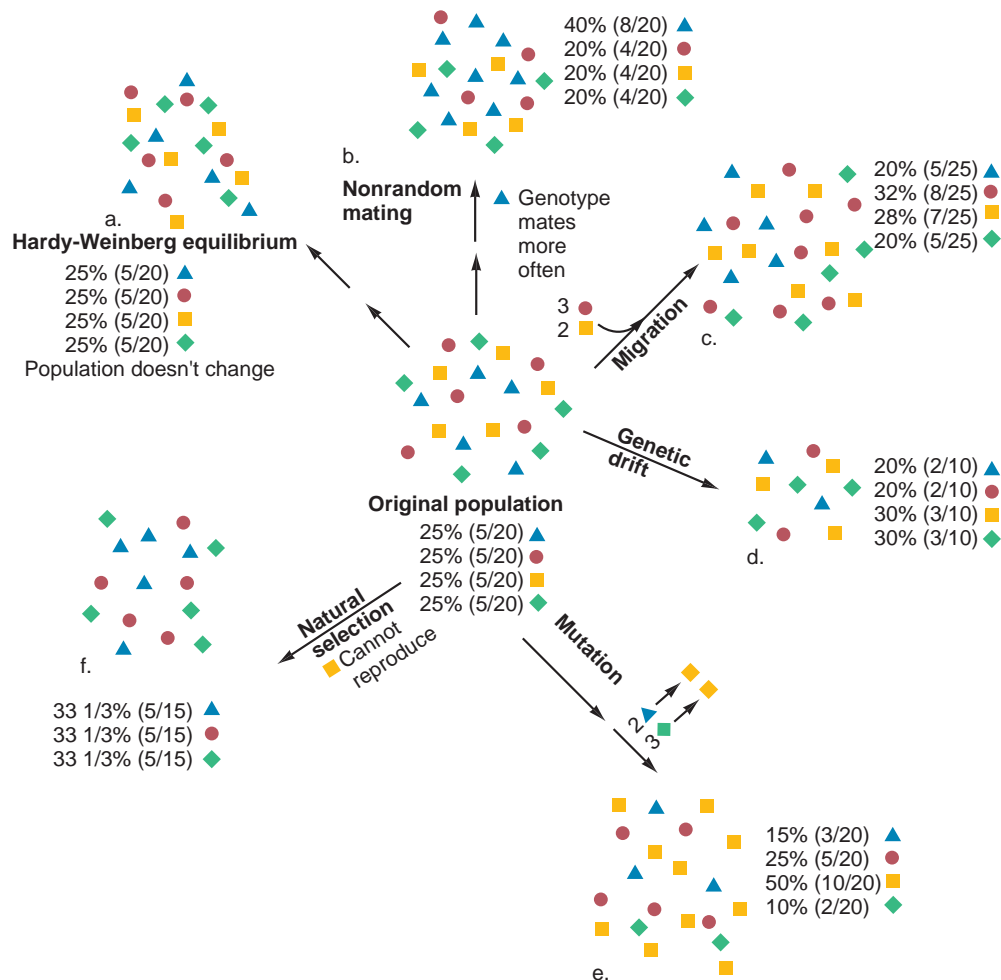
## Key Concepts

1. Because of natural selection, different alleles are more likely to confer a survival advantage in different environments. Cycles of infectious disease prevalence and virulence often reflect natural selection.
2. Balanced polymorphism is a type of natural selection in which a particular disease-causing allele is maintained because heterozygotes resist a certain infectious illness or environmental condition.

## 15.6 Putting It All Together: PKU Revisited

This chapter has discussed how monitoring allele frequencies in populations can reveal the effects of nonrandom mating, migration, genetic drift, mutation, and natural selection on evolution. **Figure 15.13** visually reviews and summarizes the forces acting alone, and **table 15.6** lists the examples used in the chapter with the mechanisms that they illustrate. These forces can interact in complex ways, and often, historical, archeological, and linguistic evidence can help us to understand these interactions. Consider, again, PKU.

The diversity of PKU mutations suggests that the disease has arisen more than once. Mutations common to many groups of people probably represent more ancient mutations that occurred before groups spread into separate populations. In contrast, mutations found only in a small geographical region are more likely to be of recent origin, perhaps



**Figure 15.13** Forces that change allele frequencies.

sequestered by genetic drift. These mutations have had less time to spread. For example, Turks, Norwegians, French Canadians, and Yemeni Jews have their own PKU alleles. Analysis of the frequencies of PKU mutations in different populations, plus logic, can reveal the roles that genetic drift, mutation, and balanced polymorphism have played in maintaining the mutation.

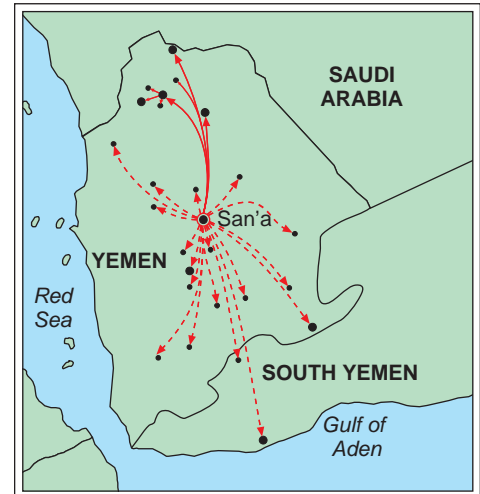
A high mutation rate cannot be the sole reason for the continued prevalence of PKU because some countries, such as Denmark, continue to have only one or two mutations. If the gene were unstable, so that it mutated frequently, all populations would have several different types of PKU mutations. This is not so.

In some isolated populations, such as French Canadians and Yemeni Jews, migration and the founder effect have maintained certain PKU alleles. In most populations, point mutations in the phenylalanine hydroxylase (*PAH*) gene cause PKU.

However, all Yemeni Jews in Israel who have PKU have a 6,700-base deletion in the third exon of the *PAH* gene—quite a different mutation. This mutation spread from northern Africa to Israel. To demonstrate this, researchers tested for the telltale deletion in the grandparents of the 22 modern Yemeni Jewish families with PKU in Israel. In the detailed court and religious records were clues pointing to San'a, the capital of Yemen. The earliest records identify two families with PKU in San'a, and indicate the mutation in one person, before 1800. By 1809, religious persecution and hard economic times led nine families carrying the mutation to migrate north and settle in three towns (**figure 15.14**). Four of the families then moved farther northward, into four more towns. Twenty more families spread from San'a to inhabit 17 other towns. All of this migration took place from 1762 through the mid-1900s, and eventually led to Israel.

## Chapter Review

Mechanism of Allele Frequency Change	Examples
Nonrandom mating	Agriculture Cape population and Arnold Hopi Indians with albinism Genghis Khan's Y chromosome Rape in Darfur
Migration	Consanguinity Galactokinase deficiency in Europe ABO blood type distribution Clines along the Nile and in Italy
Genetic drift	
Founder effect	Fumarate deficiency in Arizona/Utah <i>BRCA1</i> breast cancer in French Canadians Dunkers Old Order Amish and Mennonites Afrikaners and porphyria variegata Pingelapese blindness
Population bottleneck	Cheetahs Chmielnicki massacre Chapters 12 and 13 Lactose intolerance TB incidence and virulence HIV infection Antibiotic resistance Sickle cell disease and malaria Prion disease and cannibalism CF and diarrheal disease
Mutation	
Natural selection	



**Figure 15.14 The origin of PKU.** The deletion in Israeli Yemeni Jews probably arose in San'a, Yemen, in the mid-eighteenth century. The allele spread northward as families moved from San'a in 1809 (solid arrows) and subsequently spread to other regions (broken arrows). Source: Data from Smadar Avigad, et al., A single origin of phenylketonuria in Yemenite Jews, *Nature* 344:170, March 8, 1990.

## Key Concepts

1. PKU originated more than once.
2. Genetic drift, balanced polymorphism, and perhaps mutation have affected its prevalence.

# Summary

## 15.1 Nonrandom Mating

1. Hardy-Weinberg equilibrium assumes all individuals mate with the same frequency and choose mates without regard to phenotype. This rarely happens. We choose mates based on certain characteristics, and some people have many more children than others.
2. DNA sequences that do not cause a phenotype important in mate selection or reproduction may be in Hardy-Weinberg equilibrium.
3. Consanguinity increases the proportion of homozygotes in a population, which may

lead to increased incidence of recessive illnesses or traits.

## 15.2 Migration

4. **Clines** are changes in allele frequencies from one area to another.
5. Clines may reflect geographical barriers or linguistic differences and may be either abrupt or gradual.
6. Human migration patterns through history explain many cline boundaries. Forces behind migration include escape from persecution and a nomadic lifestyle.

## 15.3 Genetic Drift

7. **Genetic drift** occurs when a small population separates from a larger one, and or its members breed only among themselves, perpetuating allele frequencies not characteristic of the larger population due to chance sampling.
8. A **founder effect** occurs when a few individuals found a settlement and their alleles form a new gene pool, amplifying their alleles and eliminating others.
9. A **population bottleneck** is a narrowing of genetic diversity that occurs after many members of a population die and the few survivors rebuild the gene pool.

## 15.4 Mutation

10. Mutation continually introduces new alleles into populations. It occurs as a consequence of DNA replication errors.
11. Mutation does not have as great an influence on disrupting Hardy-Weinberg equilibrium as the other factors.
12. The **genetic load** is the collection of deleterious alleles in a population.

## 15.5 Natural Selection

13. Environmental conditions influence allele frequencies via **natural selection**. Alleles that do not enable an individual to reproduce in a particular environment are selected against and diminish in the population, unless conditions change. Beneficial alleles are retained.
14. In **balanced polymorphism**, the frequencies of some deleterious alleles are maintained

when heterozygotes have a reproductive advantage under certain conditions.

## 15.6 Putting It All Together: PKU Revisited

15. Frequencies of different mutations in different populations provide information on the natural history of alleles and on the relative importance of nonrandom mating, genetic drift, and natural selection in deviations from Hardy-Weinberg equilibrium.

# Review Questions

1. Give examples of how each of the following can alter allele frequencies from Hardy-Weinberg equilibrium:
  - a. nonrandom mating
  - b. migration
  - c. a population bottleneck
  - d. mutation
2. Explain the influence of natural selection on
  - a. the virulence of tuberculosis.
  - b. bacterial resistance to antibiotics.
  - c. the changing degree of genetic diversity in an HIV population during infection.
3. Why can increasing homozygosity in a population be detrimental?
4. How might a mutant allele that causes an inherited illness in homozygotes persist in a population?
5. Give an example of an inherited disease allele that protects against an infectious illness.
6. Explain how table 15.2 indicates that genetic drift has occurred among the Dunkers.
7. How does a founder effect differ from a population bottleneck?
8. Describe two scenarios in human populations, one of which accounts for a gradual cline, and one for an abrupt cline.
9. How do genetic drift, nonrandom mating, and natural selection interact?
10. Define:
  - a. founder effect
  - b. balanced polymorphism
  - c. genetic load
11. How does a knowledge of history, sociology, and anthropology help geneticists to interpret allele frequency data?

# Applied Questions

1. Begin with the original population represented at the center of Figure 15.13, and deduce the overall, final effect of the following changes:
  - Two yellow square individuals join the population when they stop by on a trip and stay awhile.
  - Four red circle individuals are asked to leave as punishment for criminal behavior.
  - A blue triangle man has sex with many females, adding five blue triangles to the next generation.
  - A green diamond female produces an oocyte with a mutation that results in adding a yellow square to the next generation.
  - A new infectious disease affects only blue triangles and yellow squares, removing two of each from the next generation.
2. Before 1500 A.D., medieval Gaelic society in Ireland isolated itself from the rest of Europe, physically as well as culturally. Men in the group are called “descendants of Niall,” and they all share a Y chromosome inherited from a single shared ancestor. In the society, men took several partners, and sons born out of wedlock were fully accepted. One male, for example, Lord Turlough O'Donnell, had 10 wives and concubines, who gave him 18 sons and 59 grandsons. Today, in a corner of northwest Ireland, 1 in 5 men has the “descendant of Niall” Y chromosome. In all of Ireland, the percentage of Y chromosomes with the Niall signature is 8.2 percent. In western Scotland, where the Celtic language is similar to Gaelic, 7.3 percent of the males have the telltale Niall Y. In the U.S., among those of European descent, it is 2 percent. Worldwide, the Niall Y chromosome makes up only 0.13 percent of the total. What concept from the chapter do the data illustrate?
3. Fred Schnee, who teaches human genetics at Loras College in Iowa, offers a good example of genetic drift: seven castaways are shipwrecked on an island. The first mate has blue eyes, the others brown. A coconut falls on the first mate, killing him. The coconut accident is a chance event affecting a small population. Explain how this event would affect allele frequency, and offer another example of genetic drift.
4. The Old Order Amish of Lancaster, Pennsylvania have more cases of polydactyly (extra fingers and toes) than the rest of the world combined. All of the affected individuals descend from the same person, in whom the dominant mutation originated. Does this illustrate a population bottleneck, a founder effect, or natural selection? Give a reason for your answer.
5. Predict how natural selection might affect the frequency of alleles that protect against



- HIV infection in Africa a century from now, based on what you know about TB.
6. The *MDR1* gene encodes the protein portion of a glycoprotein (called P-glycoprotein) that dots the surfaces of intestinal lining cells and T lymphocytes. An *MDR1* allele that is overexpressed became prevalent in West Africans because the encoded protein enables cells to pump out toxins, such as those produced when bacteria contaminate food. Although these people rarely have stomachaches, HIV drugs have little effect on them. If HIV infection continues to spread in West Africa, but food poisoning becomes less common as people learn to fully cook their food, what effect will natural selection have on this gene?
  7. Which of the forces that affect allele frequencies (nonrandom mating, migration, genetic drift, mutation, and natural selection) have also acted upon populations of domesticated cats or dogs? Select a favorite type of dog or cat and describe why one of its endearing features might not have been preserved through natural selection.
  8. About half of the Melanesian people of Papua New Guinea are resistant to malaria and have shortened glycophorin C proteins, which are on the surfaces of their red blood cells. These people are homozygous recessive for a deletion in part of the gene. One way the malaria parasite enters red blood cells is through the glycophorin C proteins. Normally, the protein anchors the plasma membrane to the cytoskeleton. However, because other proteins do this, too, being homozygous recessive for the glycophorin C deletion mutation does not affect health. Is this an example of balanced polymorphism? Give a reason for your answer.
  9. The ability to taste bitter substances is advantageous in avoiding poisons, but might keep people from eating bitter vegetables that contain chemicals that protect against cancer. Devise an experiment, perhaps based on population data, to test either hypothesis—that the ability to taste bitter substances is either protective or harmful.
  10. Many people think that evolution is the transformation of one species into another, such as chimpanzees to humans, and is “just a theory.” State the genetic definition of microevolution, and give three examples, either from the chapter or from the news, that show evolution going on right now.
  11. The high prevalence of Tay-Sachs disease among the Ashkenazim before genetic testing was once attributed to balanced polymorphism in which being a carrier protects against respiratory infections. This hypothesis arose from the observation that survivors of the Warsaw ghetto, where Jews were massacred during World War II, did not die from TB and other respiratory infections as frequently as other people did. A recent study, however, found that the high incidence of Tay-Sachs disease is due to genetic drift, not balanced polymorphism. The evidence is that a dozen other genetic diseases are equally prevalent in the Ashkenazim. How does this evidence argue against balanced polymorphism?
  12. A mutation that removes the receptor for HIV on human cells also blocks infection by the bacterium that causes plague. Seven centuries ago, in Europe, the “Black Death” plague epidemic increased the protective allele in the population. Today it makes 3 million people in the United States and the United Kingdom resistant to HIV infection. Is the increase in incidence of this allele due to nonrandom mating or natural selection?
  13. Use the information in chapters 14 and 15 to explain why
    - a. porphyria variegata is more prevalent among Afrikaners than other South African populations.
    - b. many people among the Cape population in South Africa lose their teeth before age 20.
    - c. cystic fibrosis and sickle cell disease remain common.
    - d. the Pima Indians have an extremely high incidence of type 2 diabetes.
    - e. the Amish in Lancaster County and certain Pakistani groups have a high incidence of genetic diseases that are very rare elsewhere.
    - f. the frequency of the allele that causes galactokinase deficiency varies across Europe.
    - g. mitochondrial DNA sequences vary gradually in populations along the Nile River valley.
    - h. disease-causing *BRCA1* alleles are different in Jewish people of eastern European descent and African Americans.
  14. Which principles discussed in this chapter do the following classic science fiction plots illustrate?
    - a. In *When Worlds Collide*, the Earth is about to be destroyed. One hundred people are selected to colonize a new planet.
    - b. In *The Time Machine*, set in the distant future on Earth, one group of people is forced to live on the planet’s surface while another group is forced to live in caves. Over many years, they come to look and behave differently. The Morlocks that live below ground have dark skin, dark hair, and are very aggressive, whereas the Eloi that live above ground are blond, fair-skinned, and meek.
    - c. In *Children of the Damned*, all of the women in a small town are suddenly made pregnant by genetically identical beings from another planet.
    - d. In *The War of the Worlds*, Martians cannot survive on Earth because they are vulnerable to infection by terrestrial microbes.
    - e. In Dean Koontz’s novel *The Taking*, giant mutant fungi kill nearly everyone on Earth, sparing only young children and the few adults who protect them. The human race must re-establish itself from the survivors.
  15. Treatment for PKU has been so successful that, over the past 30 years, many people who would otherwise have been profoundly mentally retarded have led normal lives and become parents. How has this treatment altered Hardy-Weinberg equilibrium for the mutant alleles that cause PKU?
  16. Ashkenazim, French Canadians, and people who live in southwestern Louisiana have a higher incidence of Tay-Sachs disease than other populations.
    - a. Each of these groups has a different mutation. How is this possible?
    - b. A controversial hypothesis proposes that the high incidence of Tay-Sachs disease and other genetic disorders that harm brain cells among the Ashkenazim reflects balanced polymorphism. Because brain cells are affected, carriers are, for reasons unknown, more intelligent and therefore had a survival advantage during periods of persecution because they could better use their wits to escape violence. What evidence might support the hypothesis?
  17. Syndrome X consists of obesity, type 2 diabetes, hypertension, and heart disease. Researchers surveyed and sampled blood

from nearly all of the 2,188 residents of the Pacific Island of Kosrae, and found that 1,709 of them are part of the same pedigree. The incidence of all of the symptoms of syndrome X is much higher in this population than for other populations. Suggest a reason for this finding, and indicate why it would be difficult to study these particular traits, even in an isolated population.

18. By which mechanisms discussed in this chapter do the following situations alter Hardy-Weinberg equilibrium?
  - a. Ovalocytosis (OMIM 166910) is caused by a beneficial mutation. A protein that anchors the red blood cell plasma membrane to the cytoplasm is abnormal, making the membrane unusually rigid. As a result, the parasites that cause malaria cannot enter the red blood cells of individuals with ovalocytosis.
  - b. In the mid-1700s, a multitoed male cat from England crossed the sea and settled in Boston, where he left behind quite a legacy of kittens—about half of whom also had six, seven, eight, or even nine digits on their paws. People loved the odd felines and bred them. Today, in Boston and nearby regions, multitoed cats are far more common than in other parts of the United States.
  - c. Many slaves in the United States arrived in groups from Nigeria, which

is an area in Africa with many ethnic subgroups. They landed at a few sites and settled on widely dispersed plantations. Once emancipated, former slaves in the South were free to travel and disperse.

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 15**, and **Web Activities** to find the website link needed to complete the following activities.

19. Go to the Centers for Disease Control and Prevention website, and the journal *Emerging Infectious Diseases*. Using this resource, describe an infectious disease that is evolving, and cite the evidence for this.
20. Do a Google search for a pair of disorders listed in table 15.5 (balanced polymorphism) and discuss how the carrier status of the inherited disease protects against the second condition.

### Case Studies and Research Results

21. The human population of India is divided into many castes, and the people follow strict rules governing who can marry whom. Researchers from the University of Utah compared several genes among 265 Indians of different castes and 750 people from Africa, Europe, and Asia. The study found that the genes of higher

Indian castes most closely resembled those of Europeans, and that the genes of the lowest castes most closely resembled those of Asians. In addition, the study found that maternally inherited genes (mitochondrial DNA) more closely resembled Asian versions of those genes, but paternally inherited genes (on the Y chromosome) more closely resembled European DNA sequences. Construct an historical scenario to account for these observations.

22. The ability to digest lactose is found in several populations where dairy is part of the diet. This ability is the result of natural selection. What is the significance of the observation that different populations that can digest lactose have different alleles for the lactase gene?
23. People who have one or two alleles bearing a nonsense mutation in the *caspase-12* gene are exceptionally resistant to certain severe infections (pneumonia, diarrhea, measles, and malaria). By comparing the gene's sequence in diverse modern populations, researchers estimate that the mutation arose in Africa more than 100,000 years ago. At first the mutation remained rare, but by 60,000 years ago, when human populations were more organized and larger, the mutant allele became more common, and continues to increase in prevalence. Explain the role of natural selection in the changing allele frequency.

## A Second Look

1. How did natural selection mold the differing abilities of people to digest milk in different populations?
2. Ability to digest milk arose from positive selection. Cite an example of negative selection. (You can invent one.)
3. How can lactose intolerance be the wild type phenotype in a population?
4. Explain how geography played a role in the evolution of genes that enable people to digest cow's milk.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

3-methyl glutaconic aciduria  
type III  
Jewish genius?



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.





# Human Ancestry and Eugenics

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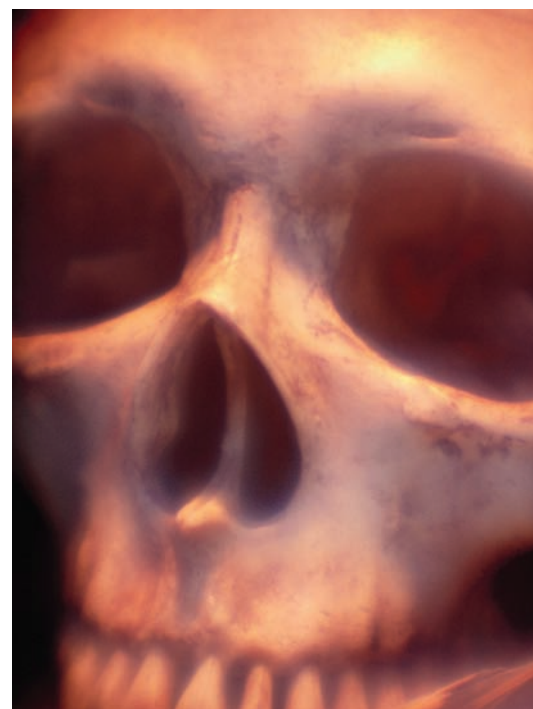
### 16.4 Eugenics

## LONELY HUMANITY

It's odd, in the animal world, to be the only ones of our kind. That wasn't always so, which may be why the theme of a dual humanity persists in science fiction. H. G. Wells's *The Time Machine* looked ahead at two battling breeds of people. In the novel *Darwin's Children*, a virus scrambles the genomes of a cohort of newborns, sowing the seeds of a new species. Other books describe holdouts from times past—a Neanderthal in modern-day Tajikistan, or a cave-man meeting a paleontologist in a Kenyan jungle.

Fossils indicate that from 2 to 6 million years ago, humans and prehumans overlapped, in time if not place. The discovery of preserved bones of several ancient humans on the island of Flores in Indonesia in 2004, however, may indicate a much more recent coexistence. Researchers discovered a female skeleton about 17 feet beneath a cave floor, with pieces of others nearby. Named *Homo floresiensis*, she became better known simply as “the hobbit,” named after a fictional character, because scientists could not agree on who and what she was. The hobbit was about half as tall as a modern human, with a brain about a third of the size. She lived about 18,000 years ago.

The combination of features of the hobbit's skeleton is unlike that of any known species. Was she a dwarf descendant of *Homo erectus*, who lived in the area 1.6 million years ago? Or was she of our own species, perhaps with microcephaly (“small head”)? Did a long-ago founder effect strand a group of very short individuals on the island, or was her small size simply similar to that of other animals isolated on islands over time? With limited resources, natural selection could gradually select bodies that need less food. More information likely lies in her genes, but so far the hot, wet conditions in Indonesia have not yielded hobbit DNA.



Comparing skulls among modern humans, our modern primate cousins, and fossilized hominids can reveal much about our ancestors and our evolution.

We have sparse evidence of our beginnings—pieces of a puzzle in time, some out of sequence, many missing. Traditionally, paleontologists (scientists who study evidence of ancient life) have consulted the record in the earth's rocks—fossils—to glimpse the ancestors of *Homo sapiens*, our own species. Researchers assign approximate ages to fossils by observing which rock layers fossils are in, and by extrapolating the passage of time from the ratios of certain radioactive chemicals in surrounding rock.

Fossils aren't the only way to peek into species' origins and relationships. Modern organisms also provide intriguing clues to the past in their DNA. Sequences of DNA change over time due to mutation, and on a population level by the forces of nonrandom mating, migration, genetic drift, and, most powerfully, natural selection. The premise of DNA comparisons is that closeness of relationship is reflected in greater similarity of sequence. The logic is that similar sequences are more likely to have arisen from individuals or species sharing ancestors than from the exact same set of spontaneous mutations occurring by chance. By analogy, it is more likely that two young women wearing the same combination of clothes and accessories purchased them at the same store than that each happened to assemble the same collection of items from different sources. On rare occasions, DNA is available from ancient specimens to add to what we know from DNA sequences of modern organisms.

Treelike diagrams are used to depict evolutionary relationships, based on fossil evidence and/or inferred from DNA sequence similarities. Branchpoints on the diagrams represent divergence from shared ancestors. Overall, evolution is shown as a series of branches as species diverged, driven by allele frequencies changing in response to the forces discussed in chapter 15: nonrandom mating, genetic drift, migration, mutation, and natural selection. Evolution is *not* a linear morphing of one type of organism into another—a common misunderstanding (**figure 16.1**). Humans and chimps diverged from a shared ancestor; humans didn't form directly from chimps. Similarly, two second cousins share great-grandparents, but one cousin did not descend from the other.

In this chapter, we explore human origins, genetic and genomic evidence for evolution, and how we attempt to alter the evolution of our own species and others.

## 16.1 Human Origins

A species includes organisms that can successfully produce healthy offspring only among themselves. *Homo sapiens* (“the wise human”), our species, probably first appeared during the Pleistocene epoch, about 200,000 years ago. Our ancestry reaches farther back, to about 60 million years ago when rodentlike insect eaters flourished. These first primates diverged to give rise to many new species. Their

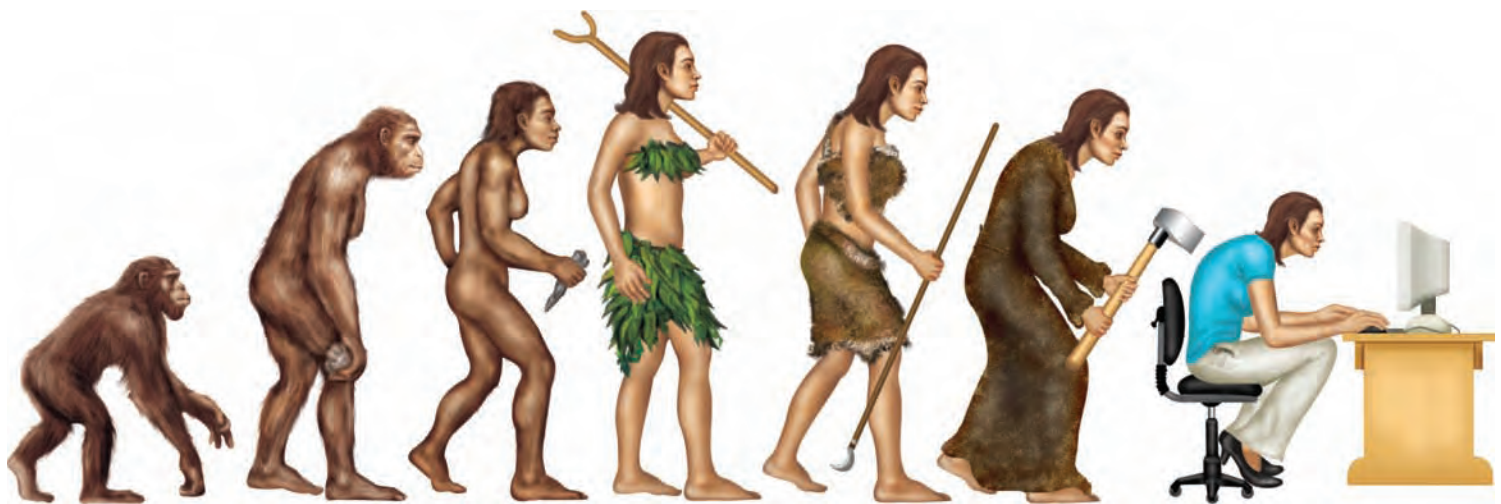
ability to grasp and to perceive depth provided the flexibility and coordination necessary to dominate the treetops.

## Hominoids and Hominins

About 30 to 40 million years ago, a monkey-like animal the size of a cat, *Aegyptopithecus*, lived in the lush tropical forests of Africa. Although the animal probably spent most of its time in the trees, fossilized remains of limb bones indicate it could run on the ground, too. Fossils of different individuals found together indicate that they were social animals. *Aegyptopithecus* had fangs it might have used for defense. The large canine teeth seen only in males suggest that males may have hunted to feed their mates. *Propliopithecus* was a monkeylike contemporary of *Aegyptopithecus*. Both animals are possible ancestors of gibbons, apes, and humans.

From 22 to 32 million years ago, Africa was home to the first **hominoids**, animals ancestral to apes and humans only. One such resident of southwestern and central Europe was called *Dryopithecus*, meaning “oak ape,” because its fossilized bones were found with oak leaves (**figure 16.2a**). The way the bones fit together suggests that this animal lived in the trees but could swing and walk farther than *Aegyptopithecus*.

More abundant fossils represent the middle-Miocene apes of 11 to 16 million years ago. These apes were about the size of a human seven-year-old and had small



**Figure 16.1** Evolution is a branching from shared ancestors. However, the very recent evolution of hominins appears as a single line of descent—one branch—because we are the only modern people. Cartoonists have drawn several variations on the evolutionary theme, often oversimplifying it, as here. The tree in figure 16.3 is more accurate.

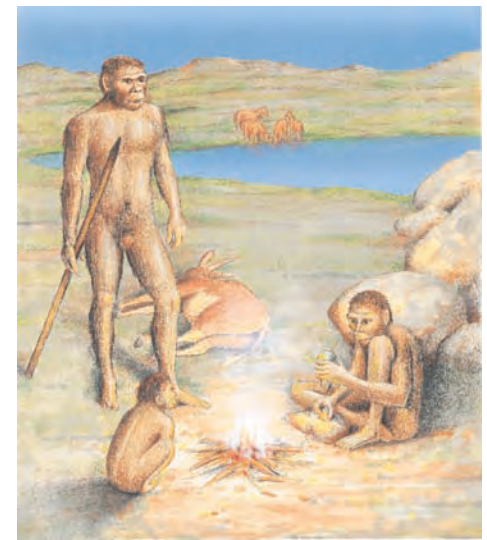




a. *Dryopithecus*



b. *Australopithecus*



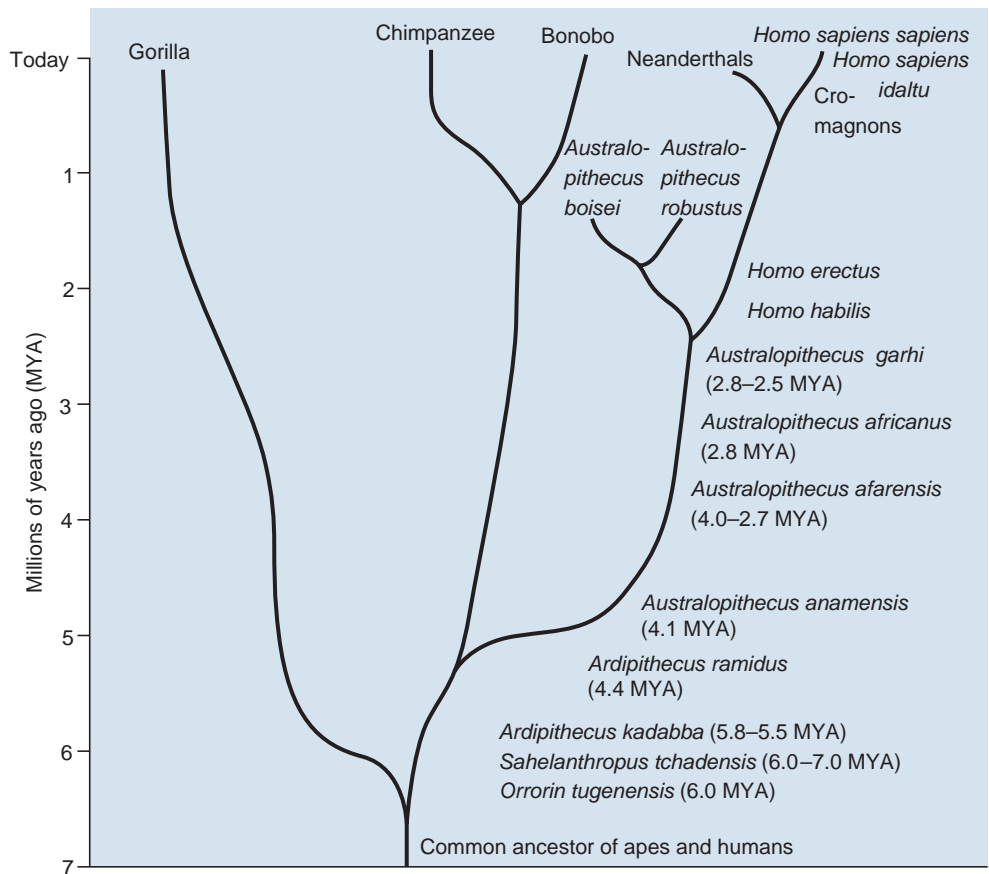
c. *Homo erectus*

**Figure 16.2 Human forerunners.** (a) The “oak ape” *Dryopithecus*, who lived from 22 to 32 million years ago, was more dexterous than his predecessors. (b) Several species of *Australopithecus* lived from 2 to more than 4 million years ago, and walked upright. (c) *Homo erectus* made tools out of bone and stone, used fire, and dwelled communally in caves from 1.6 million years ago to about 35,000 years ago.

brains and pointy snouts. (Miocene refers to the geologic time period).

Apelike animals similar to *Dryopithecus* and the mid-Miocene apes flourished in Europe, Asia, and the Middle East during the same period. Because of the large primate population in the forest, selective pressure to venture onto the grasslands in search of food and habitat space must have been intense. Many primate species probably vanished as the protective forests shrank. Of all of the abundant middle-Miocene apes, one survived to give rise to humans and African apes. Eventually, animals ancestral to humans only, called **hominins**, arose and eventually thrived. (An older term is *hominid*.)

Hominoid and hominin fossils from 4 to 19 million years ago are scarce, and are often just fragments of tooth and jaw. About 6 million years ago, the hominin lineage split from the apes. There are at least three candidates for this first primate one step closer to humanity from the chimp: *Ardipithecus kadabba* from Ethiopia, *Sahelanthropus tchadensis* from Chad, and *Orrorin tugenensis* from Kenya. Note the position of these hominins at the base of the evolutionary tree diagram in **figure 16.3**, which depicts probable relationships among some of our relatives, past and present. This evolutionary tree is based on fossil evidence and DNA sequence comparisons for the modern species.



**Figure 16.3 Evolutionary tree.** An evolutionary tree diagram indicates the relationships among primates, past and present. (Not all known hominin species are indicated.)



Fossil evidence is more complete for our ancestors who lived two to four million years ago, who walked upright and conquered vast new habitats on the plains. Several species of a hominin called *Australopithecus* lived at this time, probably following a hunter-gatherer lifestyle. They were gradually replaced with members of our own genus, *Homo*. The following sections introduce a few of these ancestors known from rare fossil remains and what our imaginations can fill in.

## Australopithecus

### Peoples of the Past—The Dikika Infant, 3.3 Million Years Ago

The three-year-old had probably wandered away from her family when she had been swept up in the sudden flood 3.3 million years ago in Ethiopia. She liked to sit up in the trees ringing the large lake, where she could safely watch the antelopes and giraffes, elephants and wildebeests. She also wandered the grasslands to the small rivulets that merged into the Awash river delta, being careful to avoid crocodiles while she waded among the reeds, picking up snails and trying to catch fishes. Then one day, perhaps after seasonal rains, the girl was overcome by rushing waters and was buried in sediments in an instant. It must have happened so quickly, in sediments so thick, that her fragile bones were not shattered, and much of her skeleton remained intact.

Paleontologists discovered the top of her skull protruding from sandstone. After five years of meticulously removing the encasing stone with dental instruments under a microscope, clues to who the Dikika infant was began to emerge. The tiny, delicate bones of the child, representing *Australopithecus afarensis*, reveal characteristics of human and chimp, in a mosaic manner. Her legs were shorter but her arms were longer than ours. Her upper half looked like that of an ape, with a large, protruding lower face and neck muscles to support it. She was hairy, with arms long enough to have easily grabbed a branch, her hands and fingers curved enough to grasp and hold on. Yet her bottom half was much more like that of a human. The great toes aligned with the other toes, the hip joints and leg bones able to support an upright position and walking, although with a hunched stance because the knee joints could not lock. She had a voice

box, and while some of her teeth resembled those of apes, some were more humanlike. Her cranium was slightly larger than that of a chimp. Overall, the infant, and probably later *australopithecines*, looked like apes but walked like humans—at least part of the time.

*Australopithecines* had flat skull bases, as do all modern primates except humans. They stood about four to five feet tall. The angle of preserved pelvic bones, plus the discovery of *Australopithecus* fossils with those of grazing animals, indicate that this ape-human had left the forest.

The most ancient species of *australopithecine* known, *Australopithecus anamensis*, lived about 4.1 million years ago. A partial skeleton of a female *A. afarensis*, named

Lucy, represents an individual who lived about 3.6 million years ago in the same area as the Dikika infant (**figure 16.4**). This is the only place where fossil evidence of our ancestors spans 6 million years. Lucy died, with arthritis, at about age 20.

Other fossils offer additional clues to *australopithecine* life. Two parallel paths of humanlike footprints, preserved in volcanic ash in the Laetoli area of Tanzania, are contemporary with Lucy. A family may have left the prints, which are from a large and small individual walking close together, with a third following in the steps of the larger animal in front. Another find revealed remains of up to 13 individuals, representing perhaps two or more family groups.



a.



b.

### Figure 16.4 *Australopithecus*.

Lucy's skeleton offers many clues to what this hominin was like (**a**). About 3.6 million years ago, she walked upright in the grasses along a lake in the Afar region of Ethiopia, about six miles from where the Dikika infant would live 300,000 years later. She skimmed the shores for crabs, turtles, and crocodile eggs to eat. (**b**) An artist's interpretation of what Lucy may have looked like.

Toward the end of the australopithecine reign, *Australopithecus garhi* may have coexisted with the earliest members of *Homo*. Its fossils from the Afar region date from about 2.5 million years ago. Remains of an antelope found near the australopithecine fossils suggest butchering. The ends of the long bones had been cleanly cut with tools, the marrow removed, meat stripped, and the tongue cleanly sliced off. *A. garhi* stood about 4.5 feet tall, and like the Dikika infant and Lucy, the long legs were like those of a human, but the long arms were more like those of an ape. The small cranium and large teeth hinted at apelike ancestors.

Homo

Peoples of the Past—Idaltu Man, 156,000 Years Ago

Like the discovery of the Dikika infant, finding the skeleton of our ancestors from 156,000 years ago in the same place also began with a skull sticking up from the sediment, but it wasn't human. In 1997, University of California, Berkeley paleoanthropologist Tim White was driving by the village of Herto, along a bend of the Awash River. Seasonal rains had driven the nomadic people and their livestock away, and had cleared the ground in places. In one such bald spot, White spotted a hippopotamus skull sticking up. Near it were tools made of obsidian, a glasslike rock. A few days later he sent two students out in the 110-degree heat to explore further, and they very quickly found a humanlike skull lying on its side. The team painstakingly isolated the skull, wrapping it in a plaster "jacket" for transport to a laboratory for analysis. Soon, two other skulls were discovered. One was from another adult, and the other was a child's skull shattered and scattered into more than 200 pieces, including baby teeth. The researchers named the hominin *Homo sapiens idaltu*, which in the local language means "elder."

The most intact skull was slightly longer, and the brain slightly larger, than those of modern humans. Fine, parallel lines had been etched along the base of the skull. The dome of the skull had not been damaged, as it would have been had cannibalism been practiced. The skull was very smooth, and there were no other bones nearby. Might the skulls have been gently separated from the bodies, saved, and touched, as modern cultures do to honor the dead?

Other fossils filled in the story. Evidence of catfish and hippos indicate that the Awash River had flooded, forming a freshwater lake. The hippo and buffalo bones bore marks made with tools that had probably sliced off meat. Some bones were broken in ways that suggested that the people ate the marrow. The tools were of a sophisticated design compared to the flaked tools from a million years ago. Overall, the scene evoked an image of ancestors who not only understood the concept of death, but who practiced mortuary rituals.

Our knowledge of how *Homo* replaced *Australopithecus* is sparse. Some australopithecines were "dead ends" that died off. Clues suggest that by 2.3 million years ago, *Australopithecus* coexisted with *Homo habilis*—a more humanlike cave dweller who cared intensively for its young. *Habilis* means handy, and this primate was the first to use tools for tasks more challenging than stripping meat from bones. *H. habilis* may have descended from hominins who ate a greater variety of foods than other ape-humans, allowing them to live in a wider range of habitats.

*H. habilis* coexisted with and was followed by *Homo erectus* during the Paleolithic Age (table 16.1). One famed *H. erectus* fossil, named "Daka" for the place where it was found in the Afar region, represents an individual who lived about a million years ago. It had a shallow forehead, massive brow ridges, a brain about a third smaller than ours, and strong, thick legs. Daka lived on a grassland, with elephants, wildebeests, hippos, antelopes, many types of pigs, and giant hyenas. Figure 16.5 depicts what he might have looked like.

*H. erectus* left fossil evidence of cooperation, social organization, tools, and use of fire. Fossilized teeth and jaws suggest that they ate meat. The distribution of fossils indicates that they lived in families of male-female pairs (most primates have harems).

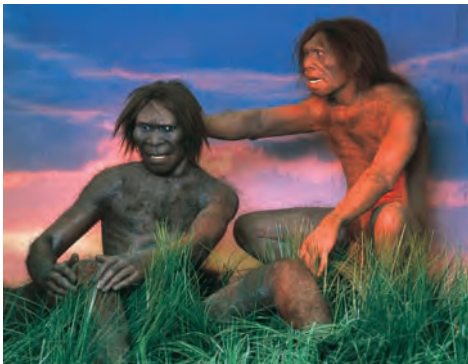


Figure 16.5 *Homo erectus*. This artist's rendition is based on many fossils.

The male hunted, and the female nurtured the young. They were the first to have an angled skull base that permitted them to produce a greater range of sounds, making speech possible. *H. erectus* is also our oldest ancestor for whom we have evidence of genetic disease, amelogenesis imperfecta (OMIM 104500), in the teeth of a fossil from Ethiopia.

*H. erectus* fossils are very widespread. They have been found in China, Java, Africa, Europe, and southeast Asia, indicating that these animals could migrate farther than earlier primates.

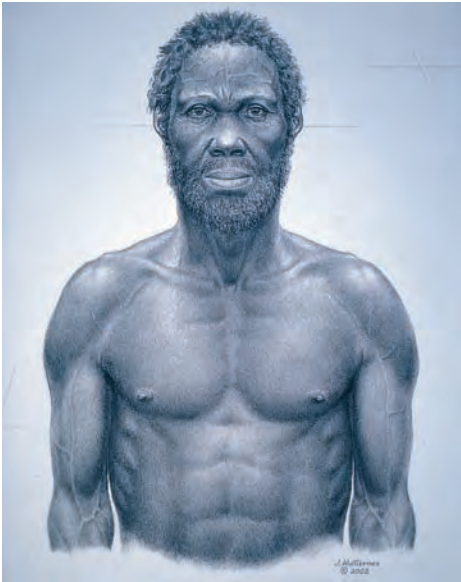
The fossils of *H. sapiens idaltu* from Ethiopia reveal that by 156,000 years ago, our ancestors did not look very different from ourselves (figure 16.6). *H. sapiens idaltu* probably resembled an Australian aborigine, with a large and powerful build and dark skin.

By 70,000 years ago, humans used more intricately carved tools made of bones, and red rock that bore highly symmetrical hatchmarks, which may indicate early counting. Groups of hominins may have been very isolated on the vast continent. Others were already leaving Africa. Because of the isolation, it's possible that even as *H. sapiens idaltu* and perhaps others yet to be discovered

Table 16.1  
Cultural Ages

Age	Time (years ago)	Defining Skills
Paleolithic	750,000 to 15,000	Earliest chipped tools
Mesolithic	15,000 to 10,000	Cutting tools, bows and arrows
Neolithic	10,000 to present	Complex tools, agriculture



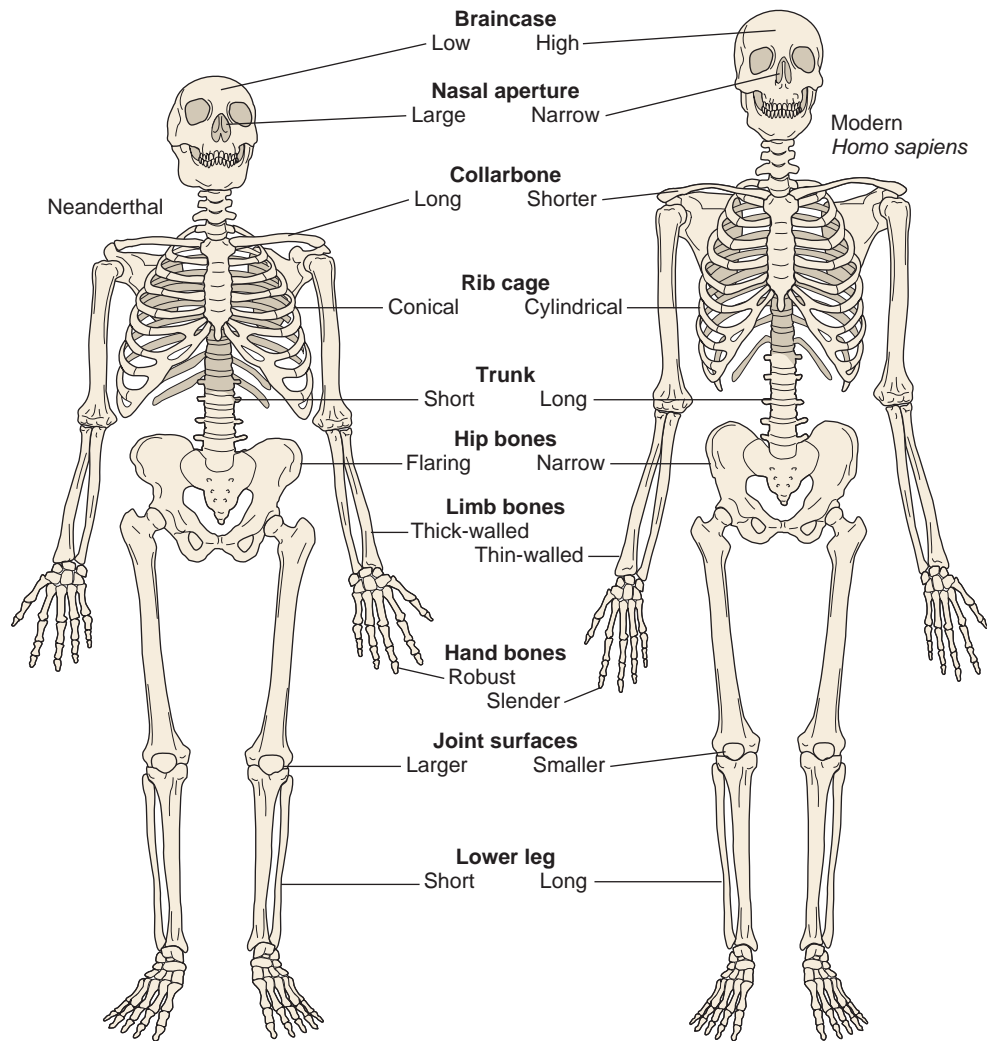


**Figure 16.6 *Homo sapiens idaltu*.** Discovery of three skulls made possible this artist's depiction of what this early member of our species might have looked like—not very much different from us.

were far along the road to modern humanity, pockets of *H. erectus* may have persisted, perhaps until as recently as 35,000 years ago.

The ill-fated Neanderthals (*Homo neanderthalensis*) were also contemporaries of *H. erectus* and members of genus *Homo*. Our knowledge of the Neanderthals comes from fossil evidence as well as analysis of DNA sequences from that evidence, discussed in the next section (figure 16.7). The last common ancestor that we share with Neanderthals lived about 706,000 years ago in Africa. Neanderthals split from the lineage that led to us about 516,000 years ago. A founding group of about 3,000 Neanderthals left Africa, traveling slowly toward Europe where, by about 150,000 years ago, they were widespread. Neanderthals and modern people may have coexisted in what is now Israel about 90,000 years ago. By 70,000 years ago, the Neanderthals had spread to western Asia.

Fossil evidence indicates that from 30,000 to 40,000 years ago, the Neanderthals coexisted with the lighter-weight, finer-boned Cro-Magnons. The newcomers had high foreheads and well-developed frontal brain regions, and signs of culture that we do not see for Neanderthals. The first Cro-Magnon fossils were found in a French cave. Five adults and a baby were arranged in what appeared to be a communal grave. Nearby were pierced seashells that may have been used as jewelry. Intricate art decorated the cave walls. In



**Figure 16.7 Neanderthals.** Neanderthals probably looked a lot like us, but there were many subtle skeletal differences. We share ancestors with Neanderthals, but they are not our direct ancestors. They are a side branch on our family tree.

contrast, the few Neanderthal graves show no evidence of ritual, just quick burial.

The most recent Neanderthals that we know of lived from 28,000 to 24,000 years ago in at least eight settlements on the small, rocky island of Gibraltar. This area is the southernmost part of Europe, and remained warm when the rest of the continent underwent ice ages. Caves there had rocky ledges that may have served as hearths, as well as high ceilings that let in light. Tools left there suggest that Neanderthals may have occupied these cozy domains, possibly on and off, for 100,000 years or longer. They shared Gibraltar with the same types of animals seen on the warm, dry Serengeti plain of Africa, and also with bears, wolves, deer, cattle, ducks, tortoises, and pine and olive trees. Food was abundant, the climate warm, and the caves protective.

The decline of the Neanderthals was once attributed to competition from the lighter and presumably smarter archaic humans that became us, but it may be equally or more likely that the Neanderthals died out because their large bodies simply did not enable them to migrate fast enough to escape environmental cooling. The fact that Neanderthals lived until as recently as 24,000 years ago, coupled with evidence that our direct ancestors lived in Europe by 32,000 years ago, suggests a timing that might have allowed breeding between the two groups.

The Neanderthals take their name from Neander Valley, Germany, where quarry workers blasting in a limestone cave on a summer day in 1856 discovered the first preserved bones. A Neanderthal discovered in France fifty years later, the “Old Man” of La Chapelle-aux-Saints, led to their common



depiction as primitive and slow-witted, stooped perhaps due to arthritis. Since then, reconstructions of other Neanderthal skeletons indicate major differences from us.

Compared to a modern human, a Neanderthal had a wider pelvis, shoulders, and ribcage, and shorter forearms and shins; prominent brow ridges, a forward-pointing face, and a sloping forehead. The characteristic heavy brow bones might have resulted from genetic drift on populations isolated in cave systems. A fossilized, deformed skeleton buried with flowers in Shanidar Cave, Iraq, reveals that the Neanderthals may have been spiritual hunter-gatherers.

## Modern Humans

### Peoples of the Past: Ötzi

In 1991, hikers in the Ötztal Alps of northern Italy discovered an ancient man frozen

in the ice (**figure 16.8**). Named Ötzi, the Ice Man was on a mountain more than 10,000 feet high 5,300 years ago when he perished. He wore furry leggings, leather suspenders, a loincloth, fanny pack, bearskin cap and cape, and sandal-like snow shoes. Berries found with him place the season as late summer or early fall. His last meal was ibex and venison.

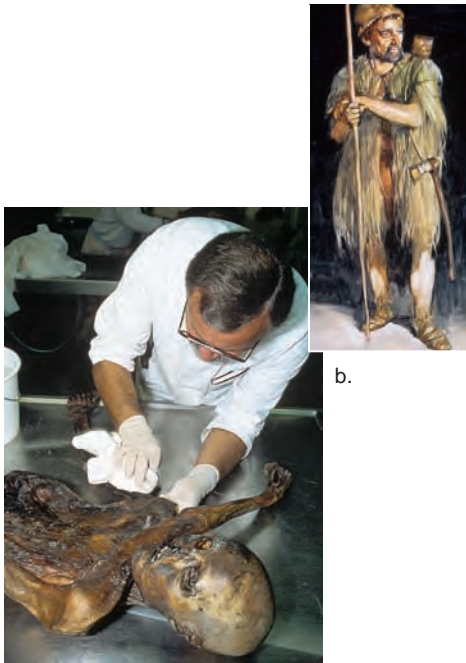
Ötzi died following a fight. He had a knife in one hand, cuts and bruises, and an arrowhead embedded in his left shoulder that nicked a vital artery. The wound bore blood from two other individuals, and his cape had the blood of a third person. He likely bled to death, falling into a ditch, where he was covered by snow. After this safe burial, which preserved his body intact, a glacier sealed the natural tomb. DNA profiling suggests that he belonged to the same gene pool as modern people living in the area, which is near the Italian-Austrian border.

Cave art from about 14,000 years ago indicates that by that time, our ancestors had developed fine hand coordination and could use symbols—milestones in cultural evolution. By 10,000 years ago, people had expanded from the Middle East across Europe, bringing agricultural practices.

Another way that anthropologists try to glimpse what humans were like a few thousand years ago is by studying vanishing indigenous peoples, such as the San (bushmen)

and pygmies of Africa, the Basques of Spain, the Etas of Japan, the Hill People of New Guinea, the Yanomami of Brazil, and another Brazilian tribe, the Arawete, who number only 130 individuals (**Figure 16.9**). Studying DNA sequences within these populations provides information on their origins. However, researchers wishing to sample DNA from these groups have run into problems when science clashes with culture. In some aboriginal societies, ancestry is extremely important, and provides the basis for identity and rights. Some people fear that genetic research might be used to dispute ancestry claims, and they are also distrustful of researchers in light of the history of other indigenous groups driven from their homes.

Yet another way to look back in time is to compare genetic diversity in modern human populations. In one landmark study, researchers compared patterns of short tandem repeats in people representing 52 populations defined by geography, language, or culture. (Recall that STRs are 2-to-10-base repeats that are not subject to natural selection because they do not affect the phenotype. An “allele” is simply the number of repeats.) The people fell into five clusters—which correspond exactly with ancient human migration patterns out of Africa.



a.

b.

**Figure 16.8 A 5,300-year-old man.** (a) Hikers discovered Ötzi, the Ice Man, in the Austrian/Italian Alps in 1991. He lived 5,300 years ago. (b) Ötzi wore well-made clothing, including a hat; used intricate arrows that demonstrate familiarity with ballistics and engineering; and carried mushrooms with antibiotic properties. He had tattoos, indentations in his ears that suggest he wore earrings, and evidence of a haircut. This depiction is derived from the evidence found on and near Ötzi’s preserved body.

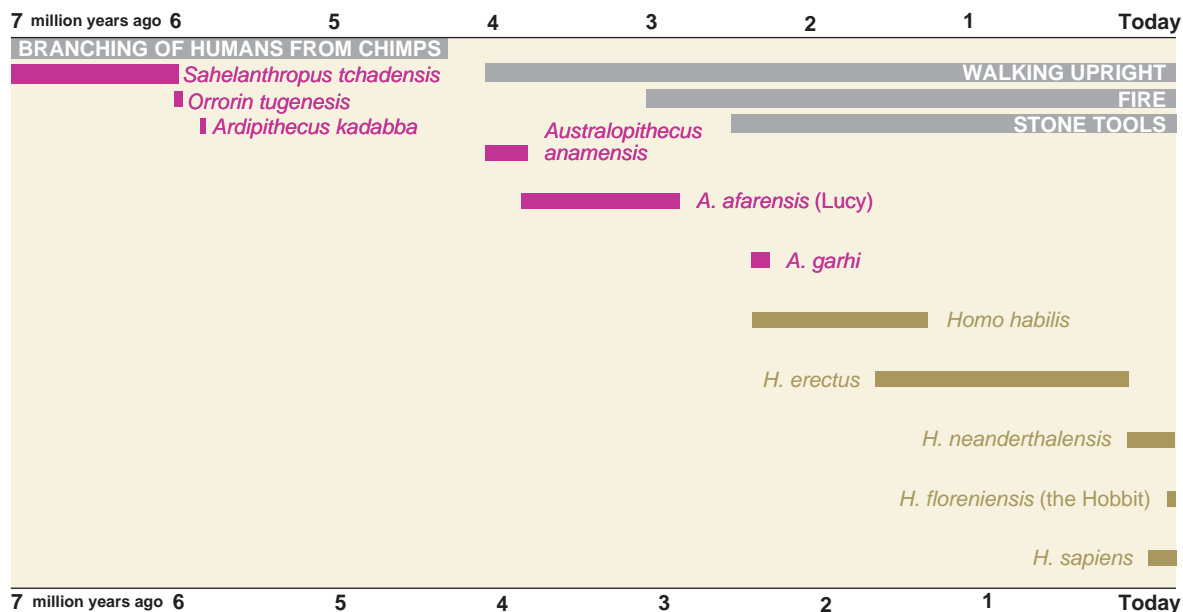


a.



b.

**Figure 16.9 Indigenous peoples hold clues—genetic and otherwise—to our past.** (a) The Yanomami live in Brazil and Venezuela, and were relatively untouched by the outside world until the 1960s. Studies of them since that time have been highly controversial. For example, a team led by a geneticist sampled blood to compare allelic diversity to other modern populations, but did not inform the people that the samples might be used in research after their deaths. The Yanomami religion forbids keeping tissue after a person’s death. The controversy continues as the people attempt to take back their blood samples from research labs. (b) The Malagasy live on the island of Madagascar. Their DNA, appearance, and customs reflect their dual East African and Indian ancestry.



**Figure 16.10** Our most recent ancestors.

**Figure 16.10** is a timeline representing some of the human ancestors discussed in this chapter.

## Key Concepts

1. Monkeylike *Aegyptopithecus* lived about 30 to 40 million years ago and was ancestral to gibbons, apes, and humans. The first hominoid (ape and human ancestor), *Dryopithecus*, lived 22 to 32 million years ago and may have walked onto grasslands.
2. Hominins (human ancestors) appeared about 19 million years ago.
3. About 4 million years ago, bipedalism opened up new habitats for *Australopithecus*. *A. garhi* may have coexisted with the first *Homo*.
4. By 2 million years ago, *Australopithecus* coexisted with the more humanlike *Homo habilis*. Later, *H. habilis* coexisted with *H. erectus*, who used tools in more complex societies. *H. erectus* then coexisted with *H. sapiens*. *H. sapiens idaltu* lived 156,000 years ago.
5. The Neanderthals were a side branch from modern humans who disappeared about 30,000 years ago.
6. A preserved man from 5,300 years ago is genetically like us.

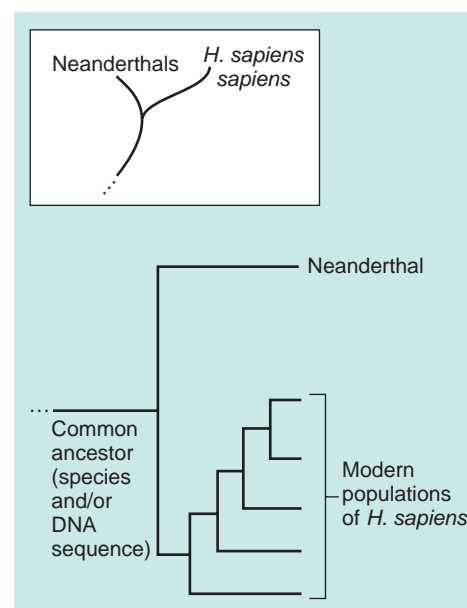
## 16.2 Molecular Evolution

Fossils paint an incomplete picture of the past because only certain parts of certain organisms were preserved, and very few have been discovered. Additional information comes from within the cell, where the informational molecules of life, DNA and amino acid sequences, change over time as mutations occur. The more alike a gene or protein sequence is in two species, the more closely related the two are presumed to be—that is, the more recently they shared an ancestor. The assumption is that it is highly unlikely that two unrelated species would evolve precisely the same sequence of DNA nucleotides by chance.

Comparing genome, DNA or protein sequences, and chromosome banding patterns constitute the field of **molecular evolution**. Knowing the mutation rates for specific genes provides a way to measure the passage of time—a sequence-based molecular clock, of sorts. Sequence information was used to build the evolutionary trees in **figure 16.11**.

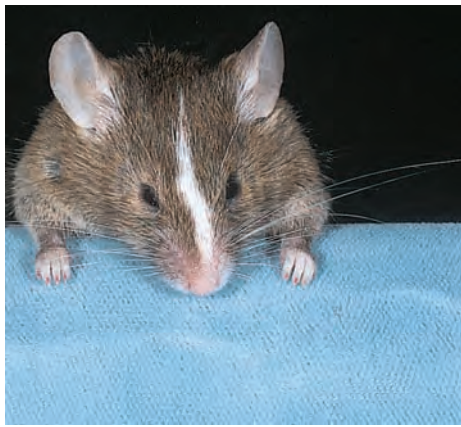
## Comparing Genes and Genomes

We can assess similarities in DNA sequences between two species for a piece of DNA, a single gene, a chromosome segment, a



**Figure 16.11** Neanderthals split from the lineage that led to *Homo sapiens*, as this molecular evolutionary tree diagram indicates. The inset shows the corresponding information on the stylized version of a tree in figure 16.3.

chromosome, mitochondrial DNA, or an entire genome. Most such efforts address evolutionary questions, but they can have practical applications, too, as figure 12.1 shows for a few animal models of human disease. Our descent from shared ancestors



a.



b.



c.

**Figure 16.12 The same mutation can cause similar effects in different species.** A mutation in mice (a), cats (b), humans (c), and other types of mammals causes light eye color, hearing or other neurological impairment, and a fair forelock.

provides the clues to ourselves in the genomes of others.

For some genes, similarities among species can be startling. People with Waardenburg syndrome (OMIM 148820), for example, have a white forelock of hair; wide-spaced, light-colored eyes; and hearing impairment (**figure 16.12**). The mutant gene is very similar in sequence in cats, horses, mice, and minks, who have light coats and eyes and are deaf. In these species, the phenotype stems from abnormal movements of pigment cells in the embryo's outermost layer.

In general, DNA sequences that encode protein are often very similar among closely related species. The related species presumably inherited the gene from a shared ancestor, and a change in that gene would not persist in a population unless it provided a selective advantage. At the same time, natural selection weeded out proteins that did not promote survival to reproduce.

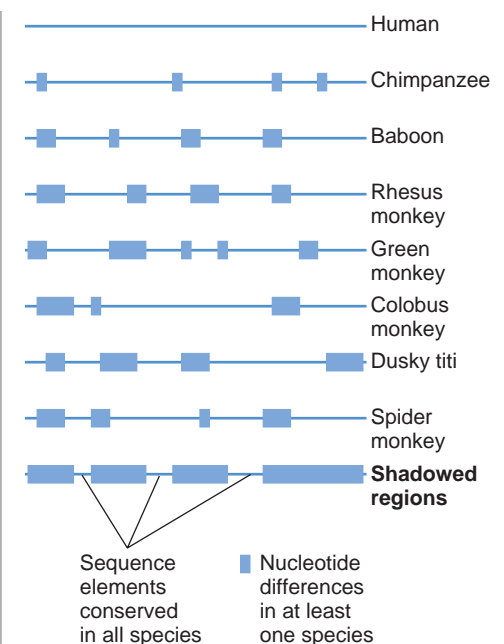
Similar DNA or amino acid sequences in different species are said to be "highly conserved." Sequences that are similar in closely related species but that do not encode protein often control transcription or translation, and so are also vital and therefore subject to natural selection. About five percent of the human genome is highly conserved, and 60 percent of these regions have known functions, so far. In contrast, some genome regions that vary widely among species do not affect the phenotype, and are therefore not subject to natural selection. Within a protein-encoding gene,

the exons tend to be highly conserved, but the introns, which are removed, are not.

The link between highly conserved sequences and evolutionary importance is not absolute. That is, some highly conserved sequences (those that are very similar in different species) do *not* have an apparent vital function, and some unconserved sequences (those that seem unique to certain species) *do* have a vital function. Even though we do not fully understand the relationships among DNA sequence conservation, biodiversity, and evolution, it is interesting to align specific genome regions that are very similar in diverse species to estimate species' relatedness, and see if the results make sense in terms of the characteristics of the organisms. This approach is called targeted comparative sequencing.

An example of a targeted comparative sequencing experiment compared counterparts of the region of human chromosome 7 that includes the cystic fibrosis gene among 17 other vertebrate species, including chimps, baboons, cats, dogs, cows, mice, rats, chickens, and pufferfish. The DNA sequence similarities paralleled phenotypic similarities and presumably evolutionary relationships. For example, for a 20,000-base portion of the *CFTR* gene, humans had 94 percent of the DNA sequence in common with baboons, and increasingly less of the sequence in common with cows, mice, and pufferfish.

In another example, comparing four genome regions among eighteen primate species revealed functions necessary to be a



**Figure 16.13 Comparing humans to their closest relatives.** For this section of a chromosome, the thin lines represent regions where the DNA sequence matches the corresponding human sequence.

Source: Reprinted with permission from Gibbs & Nelson, *Science* 299: 1331–1333 (2003). Copyright 2003 AAAS.

primate as well as DNA sequences that are unique to humans. **Figure 16.13** depicts one way to display similarities and differences among the genomes of different species.



## Solving a Problem: Comparing Chimps and Humans

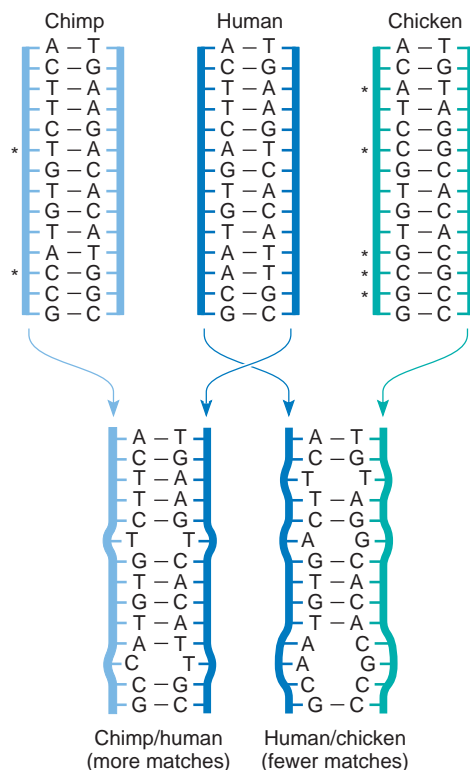
In many ways we have more in common with chimpanzees than with any other animals, but just how similar we are at the genome level depends upon how we assess similarity—for example, in terms of sequence or in terms of the numbers of copies of sequences or sequences missing from the human genome. The commonly repeated estimate of 98.7 percent sequence similarity at the genome level between human and chimp originated from studies conducted in the 1970s using a technique called DNA hybridization. DNA from two species is unwound, cut, and mixed. Complementary pieces bind, and some hybrid molecules form, with one strand of the double helix from one species, the other from the other species. The premise is that the higher the temperature required to separate hybrid double helices, the more of the sequence is shared, because more complementary base pairs attract (figure 16.14). These studies used DNA segments present in single copies in the genome, which indicates that they likely encode protein. Protein comparisons support the 98.7 percent sequence identity.

Another way that the genomes of human and chimp differ is in the number of copies of certain DNA sequences. Genome similarity can be estimated by tracking “indels,” for “insertions and deletions.” Compared to the chimp genome, the human genome has additional copies of certain sequences (“insertions”) and lacks certain sequences (“deletions”). If small insertions and deletions that distinguish the human and chimp versions of the same gene are considered, then our degree of genome similarity is only about 96.6 percent. The degree of similarity may even be as low as 94 percent if sequences not in the human genome are considered. That is, what *isn't* present defines us as well as what *is* present.

A simple calculation on a short, hypothetical DNA sequence demonstrates the effect of small differences. Consider an ancestral sequence of 15 bases:

GATACGAGCTCTAAC

“Ancestral” means that the most recent common ancestor of humans and chimps



**Figure 16.14 The rate of DNA hybridization reflects the degree of evolutionary relatedness.** This highly schematic diagram shows why DNA from a human hybridizes more rapidly with chimpanzee DNA than with chicken DNA. Each \* refers to a site where chimp or chicken DNA differs from human DNA.

had this sequence. If a single-base substitution occurred after the divergence from the shared ancestor, then the correspondence would be less than 100 percent:

Chimp GATACGAGCTCTAAC  
Human GATACGAGCTA TAAC

After the C-to-A point mutation occurs, humans and chimps share 14 of these 15 bases, for a correspondence of 93.3 percent, rather than 100 percent identity. But what happens when three bases at a time (so as not to offset the reading frame) are added or deleted in one of the evolutionary lines? Imagine that three bases inserted into the human lineage as follows:

Chimp GATACGAGCTCTAAC  
Human GATGCAACGAGCTCTAAC

The correspondence is now 15 out of 18 bases, or 83.3 percent.

If the human lineage lost three bases, the correspondence would also diminish:

Chimp GATACGAGCTCTAAC  
Human GATAGCTCTAAC

The sequence now shares 12 out of 15 bases, or 80 percent.

The similarity between the human and chimp genome decreases even more if non-coding regions, such as introns and repeats, are considered. However, differences in indels and repeats do not explain how we differ from chimps on a whole organism level. To assess phenotypic distinctions, it is more helpful to look at individual traits, some of which are determined by single genes (**Reading 16.1**). Individual genes can actually have great effects on appearance, physiology, and development.

## Genes That Help to Define Us

Uniquely human traits include spoken language, abstract reasoning ability, highly opposable thumbs, and larger frontal lobes of the brain. One stark difference between chimp and human that could stem from a single gene is hairiness. Chimpanzees and gorillas express a keratin gene whose counterpart in humans has been silenced into pseudogene status by a nonsense mutation. The protein isn't made. When our ancestors left the forests, natural selection might have favored loss of body hair to provide more efficient cooling or as a way to shed skin parasites such as lice. Speech may also be due to a single gene difference between humans and chimps. A family in London whose members have unintelligible speech led to the discovery of a single gene (*FOXP2*, OMIM 605317) that controls speaking ability—and is present, but different, in chimps.

Another single gene that accounts for great differences among primates controls the switch from embryonic to fetal hemoglobin (see figure 11.2). More primitive primates lack or have very little fetal hemoglobin. In more recently evolved and more complex primates, fetal hemoglobin correlates to lengthened fetal period, which extended the time for brain growth. With larger brains came greater skills. Single genes can also explain the longer childhood and adolescence in humans compared to chimpanzees.

Single genes that distinguish humans from chimps appear to be few, but they tend to be implicated in Mendelian disorders. Perhaps this reflects the fact that the genes that distinguish us have recently taken on their new functions, and the genome has not yet had time for protective redundancies to have evolved.

In 1975, Mary-Claire King and the late Allan Wilson, at the University of California, Berkeley, developed the “regulatory hypothesis” to explain why humans and chimps are genetically so similar, but look and behave so differently. They suggested that the key difference is in gene expression, not genome sequence. Today, DNA gene expression microarray experiments back up their hypothesis. One study contrasted gene expression in the liver and brain in the two species. The differences in the brain were far greater than in the liver. It makes sense that our livers are more alike than our brains (or at least we’d like to think so!).

Comparisons of the human genome sequence to those of other species are interesting, too. Our close relationship to the other vertebrates is revealed by comparing the human genome sequence to that of the pufferfish *Tetraodon nigroviridis*. Its genome is like ours, minus many of the repeats and introns. It is odd to think that the protein-encoding portion of our genome is nearly the same as that of a fish.

## Considering Genomes

Overall, the human genome has a more complex organization of the same basic parts as the fruit fly and roundworm genomes. For example, the human genome harbors thirty copies of the gene that encodes fibroblast growth factor, compared to two copies in the fly and worm genomes. This growth factor is important for the development of highly complex organs.

Genome studies indicate that over deep evolutionary time, genes and gene pieces provided vertebrates, including humans, with certain defining characteristics:

- complex neural networks
- blood clotting pathways
- acquired immunity
- refined apoptosis
- greater control of transcription

- complex development
- more intricate signaling within and among cells

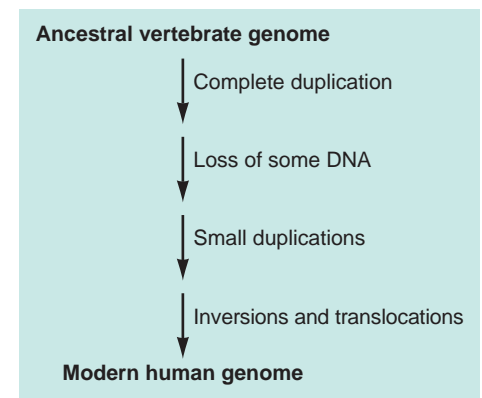
## Did the Human Genome Duplicate?

Comparing the human genome to itself provides clues to evolution, too. The many duplicated genes and chromosome segments in the human genome suggest that it doubled, at least once, since diverging from that of a vertebrate ancestor about 500 million years ago. Researchers infer what might have happened from the number and organization of the duplicated sequences. Either the human genome doubled twice, followed by loss of some genes, or, more likely, one doubling was followed by additional duplication of certain DNA sequences. Sequences of gene families (clusters of genes with similar sequences and functions) support a lone complete doubling at the dawn of vertebrate life followed by a continual replacement of about 5 to 10 percent of the genome beginning 30 to 50 million years ago.

The extensive duplication within the human genome distinguishes us from other primates. Some of the doublings are vast. Half of chromosome 20 repeats, rearranged, on chromosome 18. Much of chromosome 2’s short arm reappears as almost three-quarters of chromosome 14, and a block on its long arm is echoed on chromosome 12. The gene-packed yet tiny chromosome 22 includes eight huge duplications and several gene families.

The human genome is riddled with redundancy, but repeated DNA sequences should not be considered “junk.” Duplications provide raw material and flexibility for future evolution. A copy of a DNA sequence can mutate, allowing a cell to “try out” a new function while the old one carries on. More often, the twin mutates into a silenced pseudogene, leaving a ghost of the gene behind as a similar but untranslated DNA sequence.

A duplication can be located near the original DNA sequence it was copied from, or away from it. A sequence repeated right next to itself is called a tandem duplication, and it usually results from mispairing during DNA replication. A copy of a gene on a different chromosome may arise when messenger RNA is copied (reverse transcribed)



**Figure 16.15** The evolution of the modern human genome.

into DNA, which then inserts elsewhere among the chromosomes.

Duplication of an entire genome results in polyploidy, discussed in chapter 13. It is common in plants and some insects, but not vertebrates. (Polyploidy versus duplications can be compared to burning an entire CD versus copying only certain songs.) If a polyploid event was followed by the loss of some genes, then peppered with additional gene duplications, the result would look much like the modern human genome (figure 16.15). The remnants of such an ancient whole-genome duplication would have become further muddled with time, as inversions and translocations altered the ancestral DNA sequence.

## Ancient DNA

When comparing DNA of modern species, a researcher can easily repeat an experiment—ample samples of DNA are available directly from the sources. This isn’t so for ancient DNA, such as genetic material from insects preserved in amber, which is hardened resin from pine trees. The mix of chemicals in amber entombed whatever fell into it when it was the consistency of maple syrup. Alcohols and sugars in the resin dried out the specimen, and other organic molecules acted as fixatives, keeping cellular contents in place. The resin sealed out oxygen and bacteria, preventing decomposition. Finally, other organic molecules hardened the resin over 4 to 5 million years. Today, the DNA is extracted and amplified.

Probing ancient, preserved DNA for clues to past life is romanticized by the media. The novel and film *Jurassic Park*, for example, described cloning dinosaurs from



## Reading 16.1

# What Makes Us Human?

Comparison of the chimpanzee and human genomes has revealed “human accelerated regions.” These are highly conserved sequences (genes present in humans and apes) that show signs of positive selection in humans, such as an amino acid change seen in all human groups but not in the chimp or orangutan versions of the same gene. These genes may represent characteristics that in some way distinguish us from our closest primate relatives. Signs of positive selection in the human genome flesh out views of our ancestry from paleontology.

### Tool Use

A paleontologist enjoys a different view of the origin of humanity than that of a geneticist. University of California, Berkeley, paleontologist Tim White heads a team that, for months at a time, calls the Afar region of Ethiopia home. Here, scattered and at different levels, lie remains of our ancestors stretching back some 6 million years, teasing at the time when our forebears split from an ancestor shared with the chimpanzee.

White led the teams that discovered *Ardipithecus*, *Australopithecus garhi*, “Daka,” and *H. sapiens idaltu*. He sums up what distinguishes our species in one word: culture. His imagination takes him back in time:

**It all started about 2.5 million years ago, when guys started banging rocks together. That’s what allowed the niche to expand in the beginning, the start of culture. Tool**

**making, utilizing stone, probably began in *Australopithecus*, such as Lucy. They were very adaptable and very widespread, all over Africa. These bipeds were small-brained, and they weren’t busy becoming human, but being australopithecines. At some point, a population of that highly intelligent, bipedal generalist organism that was *Australopithecus* began to exhibit behaviors that we see in the chimp. Chimps hunt monkeys. But chimps lack tools. At some point, an early hominid didn’t lack those tools anymore, and that particular sect formed the beginning of the lineage that would ultimately diverge from other australopithecines that kept on being australopithecines, and that lineage would go on to become early *Homo*. There may have been different varieties, but eventually there was *Homo erectus*.**

### Walking

Diseases of modern humanity can reveal traits of evolutionary import. Consider Joubert syndrome (OMIM 608629). In this disorder, nerve cell fibers cannot cross from their origin on one side of the brain to the other, so a person cannot move just one arm or leg. In response to a command to move one limb—both move. The part of the brain that controls posture, balance, and coordination is compromised. The gene that causes Joubert syndrome, called *AHI1*, is identical in all modern human groups examined, but

has different alleles in chimps, gorillas, and orangutans. Perhaps in the lineage leading to humans, the gene came to control walking by making it possible to place one foot in front of the other.

### Running

*Homo erectus* distinguished itself in another key way: It could run for long distances, which specific anatomical adaptations made possible. The nuchal ligament that connects the skull to the neck became more highly developed in *H. erectus*, enabling the head to stay in place with the force of running. The leg muscles were also more highly developed than those of chimps or australopithecines, acting as springs. *H. erectus* also originated a large buttocks, whose muscles contract during running. All three of these structures are not merely the result of being able to walk, but enabled early *Homo*, and us, to run. This skill would have helped our ancestors to escape predators, find food, and locate new homes.

### A Big Brain

The difference between a big-brained human and a small-brained chimp may be a few single genes. About 2.4 million years ago, a gene called *MYH16* underwent a nonsense mutation, which prevented production of a type of muscle protein called a myosin. The mutation is seen in all modern human populations, but not in other

blood in mosquitoes trapped in amber—not a very likely scenario. In reality, researchers are sequencing the genome of woolly mammoths that were flash-frozen at high altitudes, using sequences from modern elephants as a guide. Mammoths roamed the grasslands of Siberia from 1.8 million years ago until about 11,000 years ago. Starvation following the last ice age drove their extinction, although a few isolated populations survived until about 3,800 years ago.

Biologists are searching frozen woolly mammoth remains for cell nuclei that could

yield DNA. They may attempt to conceive a mammoth by using a mammoth somatic cell nucleus to direct development in an enucleated elephant oocyte. An alternative strategy is to use mammoth sperm bearing X chromosomes to inseminate an elephant, which may give birth to a female that is half elephant, half mammoth. Some 13 or so years later, she can then be inseminated by more mammoth sperm, producing a baby that is three-quarters mammoth, and so on.

Ancient DNA was first extracted in 1990, from a 17-million-year-old magnolia leaf

entombed in amber. The quest to probe ancient DNA has sent researchers into the back rooms of museums, dusting off specimens of pressed leaves, pinned insects, and old bones and pelts, in search of nucleic acid clues to past life.

### Comparing Chromosomes

Before gene and genome sequencing, researchers recognized that similarities in chromosome banding patterns reflect





Macaque



Gorilla



Human

**Figure 1** A mutation in a single gene may have made the expansion of the human brain possible.

primates. Without this particular type of myosin, jaw development is not as great. With a diminished jaw, the bony plates of the skull could expand, allowing greater brain growth (**figure 1**). Researchers nicknamed the mutation RFT, for “room for thought.” Fossil evidence indicates that the switch from “big jaw, small brain” to “small jaw, big brain” happened when *Homo* gradually replaced *Australopithecus*, about 2 million years ago. The genetic analysis may be new, but the idea wasn’t. Charles Darwin wrote in 1871 that different-sized jaw muscles were at the root of the distinction between apes and humans.

## Cognition

At the genetic level, humans and chimps may differ more in the numbers of copies

of particular genes than in the nature of the genes. Researchers identified 134 genes with an increased copy number in the human genome compared to the genomes of the great apes. Many of these genes are involved in brain structure or function. Some of the genes promote the signal transduction that underlies long-term memory; others, when mutant, cause mental retardation or impair language skills. Single genes implicated in fueling human brain growth control the migration of nerve cells in the front of the human fetal brain.

## Sense of Smell

Natural selection retains useful traits and weeds out harmful or useless ones. Both of these forces have fine-tuned our “chemical” senses of taste and smell, actually dulling

them as our reliance on them for survival waned.

The sense of smell derives from a one-inch-square patch of tissue high in the nose that consists of 12 million cells that bear odorant receptor (OR) proteins. (In contrast, a bloodhound has 4 *billion* such cells!) Molecules given off by something smelly bind to combinations of these receptors, which then signal the brain in a way that creates the perception of an associated odor.

Our odorant receptor genes number 906, comprise about 1 percent of the genome, and occur in clusters. About 60 percent of them are pseudogenes—their sequences are similar to those of functional “smell” genes, but are riddled with mutations that prevent translation of complete proteins. Perhaps they are remnants of a distant past when we depended more upon our chemical senses for survival. Natural selection may have, over time, eliminated OR genes no longer essential to survival. Yet other genetic evidence indicates that natural selection also has acted positively to retain the OR genes that continue to function. While the pseudogenes harbor many diverse SNPs (sites where more than one base is common), the functional OR genes are remarkably alike in sequence. In addition, the nucleotide differences that persist among the retained genes actually alter the encoded amino acid, suggesting that natural selection favored these particular sequences.

evolutionary relatedness. Human chromosome banding patterns most closely match those of chimpanzees, then gorillas, and then orangutans (**table 16.2**). The karyotypes of humans, chimpanzees, and apes differ from each other mostly by inversions, which occur within chromosomes.

Chromosome banding patterns are like puzzle pieces. If both copies of human chromosome 2 were broken in half, we would have 48 chromosomes, as the three species of apes do, instead of 46. The banding pattern of chromosome 1 in humans,

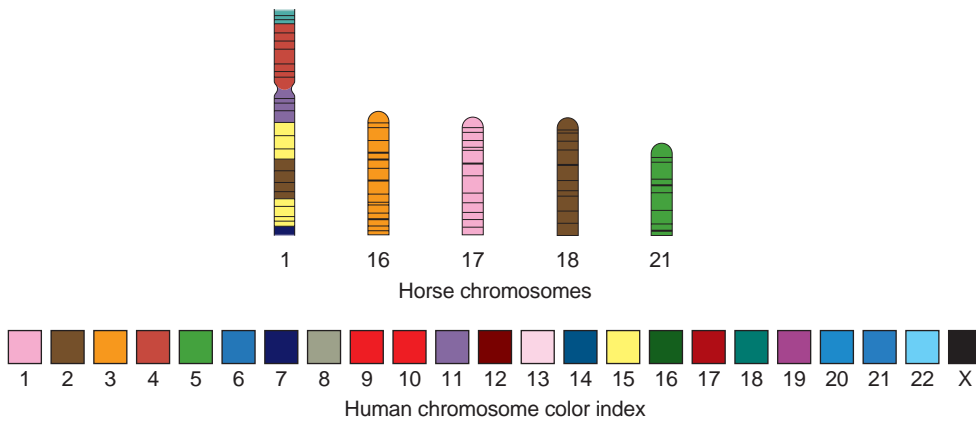
**Table 16.2**

### Percent of Common Chromosome Bands Between Humans and Other Species

Chimpanzees	99+%
Gorillas	99+%
Orangutans	99+%
African green monkeys	95%
Domestic cats	35%
Mice	7%

chimps, gorillas, and orangutans matches that of two small chromosomes in the African green monkey, suggesting that this monkey was ancestral to the other primates. Karyotype differences between these three primates and more primitive primates are predominantly translocations.

We can also compare chromosome patterns between species not as closely related. All mammals, for example, have identically banded X chromosomes. One section of human chromosome 1 that is alike in humans, apes, and monkeys is



**Figure 16.16 Comparing horse and human chromosomes.** This color-coded display of the horse genome indicates, at a glance, regions that are highly conserved. Many horse chromosomes are very similar to human chromosomes, but note that horse chromosome 1 corresponds to different human chromosomes.

also remarkably similar to parts of chromosomes in cats and mice. A human even shares several chromosomal segments with a horse (**figure 16.16**), but our karyotype is much less like that of the aardvark, the most primitive placental mammal.

Chromosome band pattern similarities, obtained with stains, are imprecise, because a band can contain many genes that differ from those within a band at a corresponding locus in another species's genome. In contrast, DNA probes used in a FISH analysis highlight specific genes (see **figure 13.9**). FISH can indicate direct correspondence of gene order, or **synteny**, between species, which is solid evidence of close evolutionary relationships. For example, 11 genes are closely linked on the long arm of human chromosome 21, mouse chromosome 16, and on a chromosome called U10 in cows. However, several genes on human chromosome 3 are found near the human chromosome 21 counterpart in mice and cows. Perhaps a mammal ancestral to these three species had all of these genes together, and the genes dispersed to an additional chromosome in humans.

## Comparing Proteins

Many different types of organisms use the same proteins, with only slight variations in amino acid sequence. The similarity of protein sequences is compelling evidence for descent from shared ancestors—that is, evolution. Many proteins in humans and chimps are alike in 99 percent of their amino acids, and several are identical. When

analyzing a gene's function, researchers routinely consult databases of known genes in many other organisms. Two of the most highly conserved proteins are cytochrome *c* and homeobox proteins.

## Cytochrome *c*

One of the most ancient and well-studied proteins is cytochrome *c*, which helps to extract energy from nutrients in the mitochondria for use in the reactions of cellular respiration. Twenty of 104 amino acids occupy identical positions in the cytochrome *c* of all eukaryotes. The more closely related two species are, the more alike their cytochrome *c* amino acid sequence is (**table 16.3**). Human cytochrome *c*, for example, differs from horse cytochrome *c* by 12 amino

**Table 16.3**

### Cytochrome *c* Evolution

Organism	Number of amino acid differences from humans
Chimpanzee	0
Rhesus monkey	1
Rabbit	9
Cow	10
Pigeon	12
Bullfrog	20
Fruit fly	24
Wheat germ	37
Yeast	42

acids, and from kangaroo cytochrome *c* by 8 amino acids. The human protein is identical to chimpanzee cytochrome *c*.

## Homeobox Proteins

A class of genes that has changed little across evolutionary time is a **homeobox** or *HOX* gene. These genes encode transcription factors that control the order in which an embryo turns on genes that ensure that anatomical parts—whether a leg, petal, or segment of a larva—develop in the appropriate places. The highly conserved portion of a homeobox protein is a 60-amino-acid sequence called the homeodomain encoded by a 180-base DNA sequence called the homeobox. (Genes that include homeobox sequences are termed *homeotic*.) Humans and most other vertebrates have 39 *HOX* genes in four clusters labeled A, B, C, and D. An intriguing aspect of *HOX* gene clusters is that the individual genes are expressed in a sequence, in developmental time or anatomical position, that mirrors their order on the chromosome.

The terms *homeobox* and *homeodomain* come from the homeotic mutants of the fruit fly *Drosophila melanogaster*, which have mixed-up body parts. *Antennapedia*, for example, has legs in place of its antennae; *proboscipedia* grows legs on its mouth. The first homeobox, sequenced in 1983, was in the fly. It was then found in many diverse species.

Mutations in homeobox genes cause human illnesses. In a form of leukemia, a homeobox mutation shifts certain white blood cell progenitors onto the wrong developmental pathway. The misguided cells retain the rapid cell division characteristic of progenitor cells, causing the cancer. DiGeorge syndrome (OMIM 188400) is also caused by a homeobox mutation. Although affected individuals hardly sprout legs from their heads, as do *Antennapedia* flies, the missing thymus and parathyroid glands and abnormal ears, nose, mouth, and throat correspond to the sites of abnormalities in the flies. **Figure 16.17** shows another human disorder caused by a mutation in a *HOX* gene.

Experiments that transfer genes of one species into cells of another reveal how highly conserved the homeobox is, implying it is essential and ancient. If a mouse version of the *Antennapedia* gene is placed into the fertilized egg of a normal fly, the adult fly grows legs on its head, expressing the





a.



b.

**Figure 16.17** A human *HOX* gene mutation causes synpolydactyly (OMIM 186000). Mutation in the *HOXD13* gene disrupts development of fingers and toes, causing a very distinctive X-ray image (a) and phenotype. (b) The third and fourth fingers are partially fused with an extra digit within the webbed material.

mouse gene as if it were the fly counterpart. The human version of the gene, placed into a mouse's fertilized egg, disrupts the adult mouse's head development. Homeotic genes and the proteins they encode, therefore, provide instructions for development of organisms whose bodies have many parts.

## Key Concepts

1. The more recently two species shared an ancestor, the more alike their DNA and protein sequences and chromosome banding patterns.
2. Targeted comparative sequencing aligns corresponding DNA sequences in different species to reveal evolutionary relationships.
3. Chimps and humans share about 98.7 percent of protein-encoding DNA, but the proportion decreases when we consider insertions, deletions, introns, and repeats. Gene expression patterns also distinguish humans from chimps. The human genome likely duplicated during its evolution.
4. DNA from preserved extinct organisms can be amplified and compared to sequences in modern species.
5. Chromosome banding pattern similarities and amino acid sequences of highly conserved proteins reflect species relationships.

## 16.3 Molecular Clocks

A clock measures the passage of time by moving its hands through a certain degree of a circle in a specific and constant interval of time—a second, a minute, or an hour. Similarly, an informational molecule can be used as a “molecular clock” if its building blocks are replaced at a known and constant rate.

The similarity of nuclear DNA sequences in different species can help scientists estimate the time when the organisms diverged from a common ancestor, if they know the rate of base substitution mutation. For example, many nuclear genes studied in humans and chimpanzees differ in 5 percent of their bases, and substitutions occur at a rate of 1 percent per 1 million years. Therefore, 5 million years have presumably passed since the two species diverged. Mitochondrial DNA (mtDNA) sequences may also be tracked in molecular clock studies, as we will soon see.

Time scales based on fossil evidence and molecular clocks can be superimposed on evolutionary tree diagrams constructed from DNA or protein sequence data. However, evolutionary trees can become

complex when a single set of data can be arranged into a large number of different tree configurations. A tree for 17 mammalian species, for example, can be constructed in 10,395 different ways! The sequence in which the data are entered into tree-building computer programs influences the tree's shape, which is vital to interpreting species relationships. With new sequence information, the tree possibilities change.

Parsimony analysis is a statistical method used to identify an evolutionary tree likely to represent what really happened. A computer connects all evolutionary tree sequence data using the fewest possible number of mutational events to account for observed DNA base sequence differences. For the 5-base sequence in **figure 16.18**, for example, the data can be arranged into two possible tree diagrams. Because mutations are rare events, the tree that requires the fewest mutations is more likely to reflect reality.

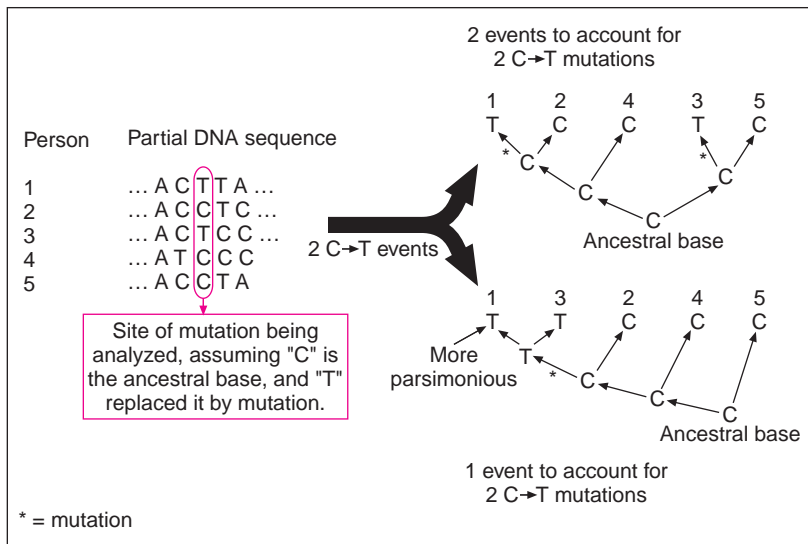
## Neanderthals Revisited

Molecular clock data can provide clues to relationships among modern organisms and also fill the gaps in the fossil record. Consider our knowledge of Neanderthals.

Two molecular technologies—analyzing ancient DNA and using mtDNA clocks—indicate that Neanderthals were a side branch on our family tree and diverged from us more than half a million years ago. This is much farther back than the 300,000 years ago that the fossil evidence indicates.

It is interesting to see how our knowledge of our relationship to Neanderthals has become more refined as more genomes are compared. The first Neanderthal DNA sequence came from several 100-base-pair-long pieces of mtDNA that do not encode protein and mutate very rapidly, perhaps because they do not affect the phenotype and are therefore not under selective pressure. That sample, analyzed in 1997, came from a bit of arm bone from the original French Neanderthal skeleton. The DNA sequences were compared to corresponding sequences from modern *Homo sapiens*, and were found to differ at 26 positions. This is three times the number of differences between pairs of the most unrelated modern humans, and the base differences were completely different from SNPs in modern human genes.





**Figure 16.18 Parsimony analysis.** Even a computer has trouble arranging DNA differences into an evolutionary tree showing species, population, or individual relationships. A parsimonious tree accounts for all data with the fewest number of mutations. Here, the two individuals who have a T in place of the ancestral C could have arisen in two mutational events or one, assuming that these individuals had a common ancestor. Since mutations are rare events, the more realistic scenario is one mutation.



**Figure 16.19 A map and DNA analysis can help trace human expansion patterns out of Africa.** Humans remained in Africa, too.

These initial results suggested that there was very little Neanderthal DNA retained in the human genome, but this only considered mitochondrial DNA. By 2006, researchers used a new DNA sequencing

technology that works especially well on fragmented DNA to analyze a million bases of Neanderthal nuclear DNA. This analysis showed that the Neanderthal chromosome that is the most different from those

of either chimp or human is the Y. Perhaps the most intriguing information will come from the DNA sequences that match for chimp and Neanderthal, but not us—these will help to define how we are different. It was the application of mutation rates to the sequence differences identified in these million DNA bases that led to the estimates of the last common ancestor living as long ago as 706,000 years ago and the split between Neanderthal and human of 516,000 years ago. The Neanderthal and human genomes are 99.5 percent identical in sequence.

## mtDNA and the Y Chromosome Hold Clues to Ancestry.

The human species arose in northeastern Africa, and spread to Australia, Asia, Europe, and the Americas. **Figure 16.19** is a general view of the migration pattern that best fits fossil, anthropological, and genetic data. To track the migrations of humanity, researchers consult mtDNA and Y chromosome sequences, which represent female and male lineages, respectively. Recall that mtDNA is passed exclusively from mothers to all offspring; Y chromosomes are unique to males. These DNA sequences have advantages beyond their gender specificity.

Mitochondrial DNA is ideal for monitoring recent events because it mutates faster than DNA in the nucleus—its sequences change by 2 to 3 percent per million years. Mutations accumulate faster in mtDNA because they are not repaired, as they are in the nucleus. mtDNA is also more abundant than nuclear DNA because a cell has many mitochondria.

An advantage of using the Y chromosome is that much of it does not recombine. Crossing over, which it could only do with an X chromosome because there is no second Y, would break the linkage from the past generation and therefore make it impossible to trace relationships. As with comparisons of other DNA sequences, the logic behind mtDNA and Y chromosome studies is that the more alike the haplotypes (closely linked variants) between two individuals or groups, the more recently they shared an ancestor. Tree diagrams depict such data.

Ancestry information from mitochondrial and Y chromosome DNA sequences often is consistent with cultural characteristics. Consider the Malagasy, an indigenous people

who live in Madagascar (see figures 16.9 and 16.19). Their mtDNA, facial features, archeology, and Indian language reflect their descent from settlers from East Africa (250 miles away) and Indonesia (4,000 miles away). Males from Borneo likely had children with females from East Africa.

## Out of Africa—The First Time

People settled Madagascar from 1,500 to 2,000 years ago. Comparing DNA sequences allows us to look back much farther than this. Theoretically, if a particular sequence of mtDNA could have mutated to yield the mtDNA sequences in modern humans, then that ancestral sequence may represent a very early human or humanlike female—a mitochondrial “Eve,” or metaphorical first woman. **Figure 16.20** shows how one maternal line may have persisted.

When might this theoretical first woman, the most recent female ancestor common to us all, have lived? In the mid 1980s, graduate student Rebecca Cann at the University of California, Berkeley, with the late Allan Wilson and Mark Stoneking compared mtDNA sequences for protein encoding as well as noncoding DNA regions in a variety of people, including Africans, African Americans, Europeans, New Guineans, Australians, and others. They concluded from several methods that the hypothesized ancestral woman lived about 200,000 years

ago, in Africa. In 2003, another research group analyzed mtDNA from 600 living East Africans, and arrived at 170,000 years ago for the beginning of the modern human line, which is remarkably close to the date of the *H. sapiens idaltu* fossils. The locations of fossil evidence, such as *H. sapiens idaltu* skulls, support an African origin, and Charles Darwin suggested it, too.

One way to reach this time estimate is by comparing how much the mtDNA sequence differs among modern humans to how much it differs between humans and chimpanzees. The differences in mtDNA sequences among contemporary humans amount to 1/25 the difference between humans and chimpanzees. The two species diverged about 5 million years ago, according to extrapolation from fossil and molecular evidence. Multiplying 1/25 by 5 million gives a value of 200,000 years ago, assuming that the mtDNA mutation rate is constant over time.

Where did Eve live? Studies comparing mt and nuclear DNA sequences consistently find that Africans have the most numerous and diverse mutations. For this to be so, Africans must have existed longer than other modern peoples, because it takes time for mutations to accumulate. In many evolutionary trees constructed by computer parsimony analysis, the individuals whose DNA sequences form the bases are from Africa. That is, gene variants in other modern human populations are all subsets of an ancestral African genome.

The idea of mitochondrial Eve is part of the “out of Africa” view, or **replacement hypothesis**, of human origins. It states that about 200,000 years ago, *H. sapiens* evolved from an *H. erectus* or other *Homo* population in Africa. This may have occurred quickly, in small, isolated pockets, or gradually across a broader swath of the continent. However it happened, eventually descendants of these early *H. sapiens* expanded.

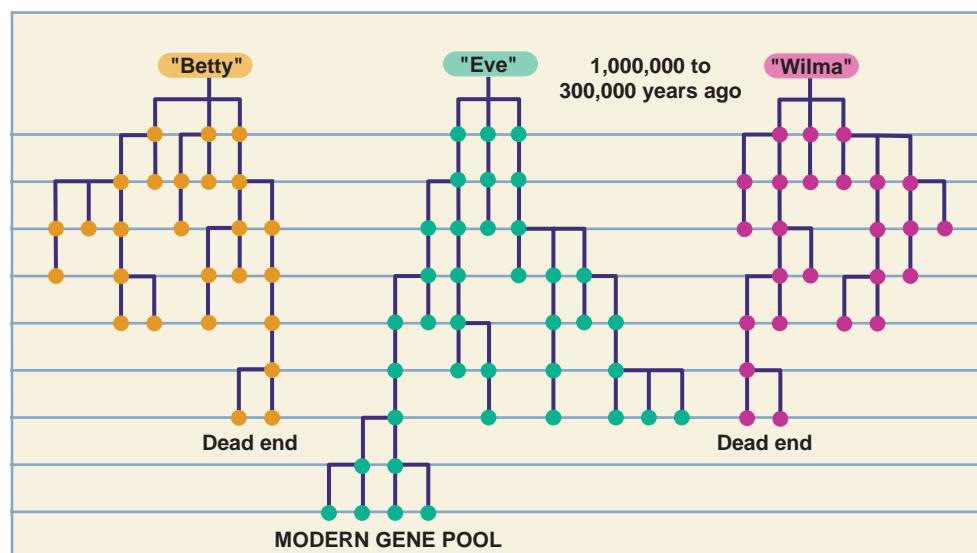
An alternate view, largely disproven, is the **multiregional hypothesis**, which maintains that human traits originated in several places, and *H. erectus* or another type of *Homo* expanded well beyond Africa, mixing and sharing genes, gradually evolving into *H. sapiens* on a global scale, without isolated pockets of peoples. (Anthropologists prefer the word “expand” to “migrate” from Africa, because although people left, many also remained, and evolution continued in Africa.) The replacement and multiregional hypotheses were once so contentious that scientists fought over them at meetings and in print.

## The African Slave Trade

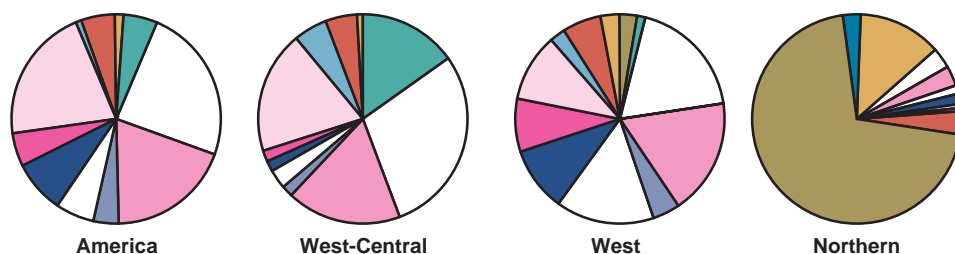
Mitochondrial DNA has been used to track a much more recent out-of-Africa event: the slave trade. From the fifteenth through the nineteenth centuries, approximately 11 million Africans were captured and sent to the Americas, as slaves. Two million died en route, as did many others in the hard years to follow. Historical records show that about two-thirds of the slaves came from western Africa, about a third from west-central Africa, and most of the remainder from southeastern Africa.

European researchers compared haplotypes spanning a several hundred base sequence of mtDNA among 481 people of recent African ancestry living in the Americas to DNA from 2,374 people from various parts of Africa. **Figure 16.21** clearly shows that the contributions from western and west-central Africa are echoed in about 90 percent of today’s African Americans.

Although the mtDNA evidence is consistent with historical records, researchers caution that it is probably not possible to trace any particular individual or family back to a specific place or ethnic group in Africa—despite several websites offering consumer mtDNA tests to trace African ancestry. Reasons range from the

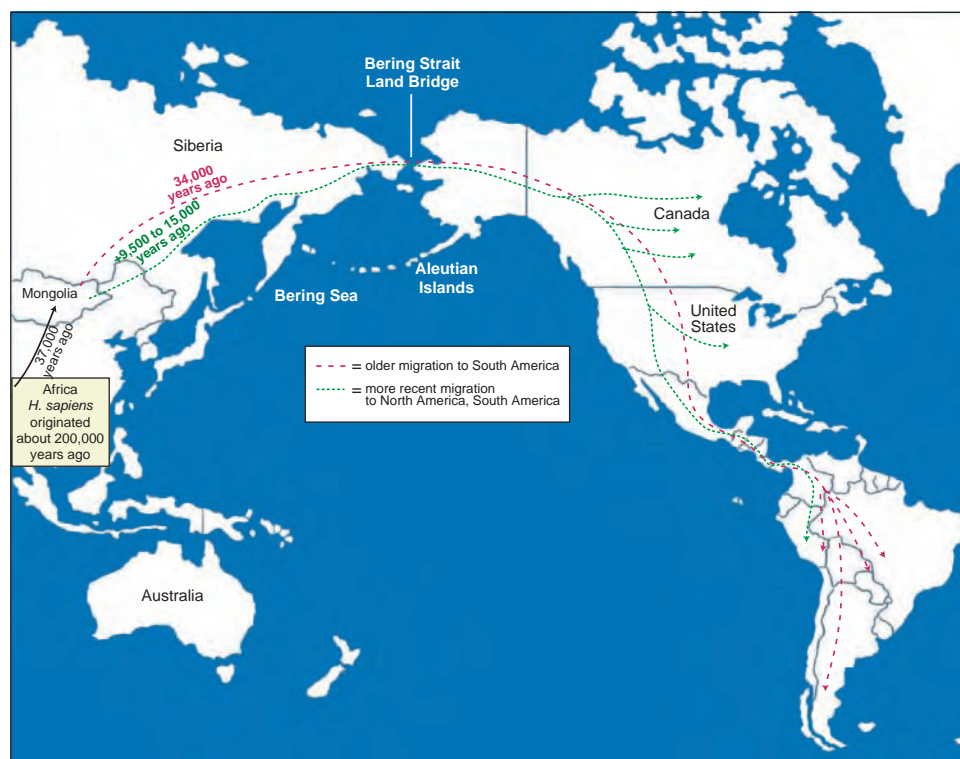


**Figure 16.20 Mitochondrial Eve.** According to the mitochondrial Eve hypothesis, modern mtDNA retains some sequences from a figurative first woman, “Eve,” who lived in Africa 300,000 to 100,000 years ago. In this schematic illustration, the lines represent generations, and the circles, females. Lineages cease whenever a woman does not have a daughter to pass on the mtDNA.



**Figure 16.21 The sources of slaves in the Americas.** Comparison of mtDNA sequences in several modern populations supports historical records of slaves coming predominantly from west and west-central Africa. Each color represents a distinct set of mtDNA sequences (haplotypes). The American pattern most closely resembles those from West-Central and West Africa. DNA ancestry tests cannot trace African Americans to specific tribes with reliability because of the degree of mixing in Africa.

Source: From “The African Diaspora: Mitochondrial DNA and the Atlantic Slave Trade” by Antonio Salas et.al. from *American Journal of Human Genetics*, March 2004, p. 458, figure 1. Copyright © 2004. Reprinted by permission of the University of Chicago Press.



**Figure 16.22 Tracing human origins.** Analyses of mitochondrial DNA and Y chromosome DNA sequences reveal that the ancestors of native Americans probably came from Mongolia in one migration.

practical to the peculiarities of African populations:

- mtDNA samples from people in many parts of Africa today aren’t available.
- Some of the haplotypes have been widespread about the African continent since prehistoric times, making them useless for tracing specific geographic areas.
- During the time of slave capture, there was a lot of migration in Africa, mixing up the haplotypes that might have defined particular groups.

## Native American Origins

Identifying the origins of Native Americans is challenging because data from linguistics, archaeology, and genetics do not always agree. A study from 1987, for example, established three waves of migration across the Bering Strait land bridge that formed between Siberia and Alaska during low glacial periods. The basis was a comparison of many Native American languages, and subsequent grouping of the people into the “Eskimo-Aleut,” who arrived 7,000 to 5,000 years ago, the

“Na-Dene,” who came 15,000 to 12,000 years ago, and the “Amerinds,” who arrived about 33,000 years ago. But only a few sounds had been used to distinguish the languages, lumping several as Amerind that may actually have been distinct in their origins. The premise for grouping the people was faulty.

Since then, several genetic studies have countered the “three migration hypothesis,” but even the genetic studies do not completely agree. One problem is that studying different parts of the human genome can yield different results, because DNA sequences change at different rates. Y chromosome analyses support one migration from 37,000 to 23,000 years ago that introduced diverse genes—but from the Mongolian/Chinese border, not Siberia. Yet mtDNA finds a long migration, from Mongolia, about 21,000 years ago (figure 16.22). Yet another study of nine genes concurs with archaeological evidence that the founding population that traveled from Asia to North America may have been as small as 80 individuals, representing about 1 percent of an ancestral population.

Even though the data support migration from Mongolia, that was probably not the sole source of people in the Americas, according to mtDNA of modern Native Americans. They have five major haplotypes, A through D and X. A through D account for 97 percent of Native Americans, who are of Asian origin. In contrast, haplotype X is not seen in Siberian people, but is found among certain European groups. It isn’t clear whether the European contribution to the Native American gene pool arrived by crossing the Atlantic, or from migrating from the other direction across Asia, over the Bering Strait.

Archaeological evidence suggests other scenarios for the peopling of the Americas. For example, a type of stone tool called a Clovis point is known in many American settlements, dating from 13,500 to 12,500 years ago. These tools are remarkably similar to tools from southwest France and northern Spain from 19,100 to 24,000 years ago, yet unlike stone tools in museums in Siberia, leading some anthropologists to envision expansion to the New World via the Atlantic ocean. This hypothesis might explain similar findings of European-style tools along the east coast of the United States, such as in Virginia and South Carolina. However, the similarity in tool



shape could be a coincidence. Another hypothesis, based on archaeological evidence in a settlement from 14,500 years ago in Monte Verde, in southern Chile, is that people came along the west coast by boat, living off of the abundant marine mammals. They could have completed the long journey over several generations.

It will be interesting to see what the analysis of human genomes from different populations reveals about our shared ancestry and how we spread from Africa around the world.

### Key Concepts

1. Molecular clocks apply mutation rates to time scales to estimate when two individuals or types of organisms most recently shared ancestors.
2. Different genes evolve at different rates. Parsimony analysis selects likely evolutionary trees from DNA data.
3. Mitochondrial DNA clocks trace maternal lineages, and Y chromosome sequences trace paternal lineages.
4. Molecular clocks have been used to examine the relationship of Neanderthals to modern humans and the origin and migrations of modern humans.

### 16.4 Eugenics

Fossil evidence, ancient DNA, and molecular clocks are useful in studying our past. We can control the future, to an extent, through reproductive choices. Some people try to control the genes in their offspring by seeking mates with certain characteristics, choosing egg or sperm donors with particular traits, or by ending pregnancies after prenatal diagnosis of a devastating inherited problem. Such choices, on a much larger scale with a different intent, constitute **eugenics**, which is the control of individual human reproductive choices to achieve a societal goal.

Sir Francis Galton coined the term eugenics, meaning “good in birth,” in 1883 to mean “the science of improvement of the human race germplasm through better breeding.” The 2,500-year-old caste system in India and the antimiscegenation laws in the United States that banned marriage between people of different races from 1930 to 1967 were clearly eugenic because they sought to control reproduction to change society. **Table 16.4** has other examples, and Bioethics: Choices for the Future on page 320 presents a personal viewpoint.

Galton’s ideas were popular for a time. Eugenics societies formed in several nations and attempted to practice his ideas in

various ways. Creating incentives for reproduction among those considered superior constitutes positive eugenics. Interfering with reproduction among those judged inferior is negative eugenics.

One vocal supporter of the eugenics movement was Sir Ronald Aylmer Fisher. In 1930, he published a book, *The Genetical Theory of Natural Selection*, which connected the concepts of Charles Darwin and Gregor Mendel and listed the basic tenets of population genetics. Natural selection and Mendelian inheritance provided a framework for eugenics. The final five chapters of Fisher’s otherwise highly regarded work tried to apply the principles of population genetics to human society. Fisher maintained that those at the top of a society tend to be “genetically infertile,” producing fewer children than the less affluent classes. This, he claimed, was the reason why civilizations ultimately topple. He offered several practical suggestions to remedy this, including state monetary gifts to high-income families for each child born to them.

Early in the twentieth century, eugenics focused on maintaining purity. One prominent geneticist, Luther Burbank, realized the value of genetic diversity at the beginning of a eugenic effort. Known for selecting interesting plants and crossing them

Table 16.4

#### A Chronology of Eugenics-Related Events

1883	Sir Francis Galton coins the term <i>eugenics</i> .
1889	Sir Francis Galton’s writings are published in the book <i>Natural Inheritance</i> .
1896	Connecticut enacts law forbidding sex with a person who has epilepsy or is “feeble-minded” or an “imbecile.”
1904	Galton establishes the Eugenics Record Office at the University of London to keep family records.
1907	First eugenic law in the United States orders sterilization of institutionalized mentally retarded males and criminal males when experts recommend it.
1910	Eugenics Record Office founded in Cold Spring Harbor, New York, to collect family and institutional data.
1924	Immigration Act limits entry into the United States of “idiots, imbeciles, feeble-minded, epileptics, insane persons,” and restricts immigration to 7 percent of the U.S. population from a particular country according to the 1890 census—keeping out those from southern and eastern Europe.
1927	Supreme Court ( <i>Buck vs. Bell</i> ) upholds compulsory sterilization of the mentally retarded by a vote of 8 to 1, leading to many state laws.
1934	Eugenic sterilization law of Nazi Germany orders sterilization of individuals with conditions thought to be inherited, including epilepsy, schizophrenia, and blindness, depending upon rulings in Genetic Health Courts.
1939	Nazis begin killing 5,000 children with birth defects or mental retardation, then 70,000 “unfit” adults.
1956	U.S. state eugenic sterilization laws are repealed, but 58,000 people have already been sterilized.
1965	U.S. immigration laws reformed, lifting many restrictions.
1980s	California’s Center for Germinal Choice established, where Nobel Prize winners can deposit sperm to inseminate selected women.
1990s	In the U.S., state laws passed to prevent health insurance or employment discrimination based on genotype.
2003	Many governments recommend certain genetic tests, and have legislation to prevent genetic discrimination. In the U.S., protective legislation is still in discussion.
2004	Genocide of black Africans occurs in Sudan.
2008	Federal genetic anti-discrimination legislation finalized in U.S.



# Bioethics: Choices for the Future

## Two Views of Neural Tube Defects

Genetic tests enable people to make reproductive choices that can alter allele frequencies in populations. Identifying carriers of a recessive illness, who then may decide not to have children together, is one way to remove disease-causing alleles from a population. Screening pregnant women for fetal anomalies, then terminating affected pregnancies, also alters disease prevalence and, if the disorder has a genetic component, allele frequencies. This is the case for neural tube defects (NTDs), which are multifactorial.

An NTD forms at the end of the first month, when the embryo's neural tube does not completely close. An opening in the head (anencephaly) usually ends in miscarriage, stillbirth, or a newborn who dies within days. An opening in the spinal cord (spina bifida) causes paralysis but the person can live into adulthood and have normal intelligence. Surgery can help.

In 1992, the Centers for Disease Control and Prevention concluded that taking the vitamin folic acid in pregnancy lowers the risk of NTD recurrence from 3 to 4 percent to 1.5 to 2 percent. Women who had had an affected child began taking large doses before conception. But when epidemiologists tried to monitor how well it was working, they faced a problem—prevalence of NTDs was greatly underestimated. This happened because the statistics on NTD prevalence—vital to discovering whether folic acid was preventing the defect—included only newborns, stillborns, and older fetuses. Most reports did not account for pregnancies terminated following pre-

natal diagnosis. These pregnancies caused the underreporting of anencephaly by 60 to 70 percent, and of spina bifida, by 20 to 30 percent in some states.

### A Personal View

Blaine Deatherage-Newsom has a different view of population screening for NTDs because he has one (**figure 1**). Blaine was born in 1979 with spina bifida. Paralyzed from the armpits down, he has endured much physical pain, but he has also achieved a great deal. While in high school, he put the question, "If we had the technology to eliminate disabilities from the population, would that be good public policy?" on the Internet—initiating a global discussion. He wrote:

**I was born with spina bifida and hydrocephalus. I hear that when parents have a test and find out that their unborn child has spina bifida, in more than 95 percent of the cases they choose to have an abortion. I also went to an exhibit at the Oregon Museum of Science and Industry several years ago where the exhibit described a child born with spina bifida and hydrocephalus, and . . . asked people to vote on whether the child should live or die. I voted that the child should live, but when I voted, the child was losing by quite a few votes.**

**When these things happen, I get worried. I wonder if people are saying that they think the world would be a better place without me. I wonder if people just think the lives of people with disabilities are so full of misery**



**Figure 1** Blaine Deatherage-Newsom.

**and suffering that they think we would be better off dead. It's true that my life has suffering (especially when I'm having one of my 11 surgeries so far), but most of the time I am very happy and I like my life very much. My mom says she can't imagine the world without me, and she is convinced that everyone who has a chance to know me thinks that the world is a far better place because I'm in it.**

Today Blaine works for a not-for-profit organization that refurbishes computer equipment for community service organizations.

Excerpt by Blaine Deatherage-Newsom, "If we could eliminate disabilities from the population, should we? Results of a survey on the Internet." Reprinted by permission.

to breed plants with useful characteristics, such as less prickly cacti and small-pitted plums, Burbank in 1906 applied his agricultural ideas to people. In a book called *The Training of the Human Plant*, he encouraged immigration to the United States so that advantageous combinations of traits would appear as the new Americans interbred. Burbank's plan ran into problems, however, at the selection stage, which

allowed only those with "desirable" traits to reproduce.

On the East Coast of the United States, Charles Davenport led the eugenics movement. In 1910, he established the Eugenics Record Office at Cold Spring Harbor, New York. There he headed a massive effort to compile data from institutions, prisons, circuses, and general society. In the rather simplistic view of genetics at the time,

he attributed nearly every trait to a single gene. "Feeble-mindedness," he thought, was inherited as an autosomal recessive trait. Feeble-mindedness was a catch-all phrase for a person with low intelligence (as measured on an IQ test) and such abnormalities as "criminality," "promiscuity," and "social dependency." In one famous case, a young woman named Carrie Buck was ordered to be sterilized when she, her mother, and her illegitimate



infant daughter Vivian were declared feeble-minded. Carrie had been raped by a relative of her foster parents, and was actually an average student. **Figure 16.23** shows the pedigree for Carrie Buck and her “inherited trait” of feeble-mindedness.

Other nations practiced eugenics. From 1934 until 1976, the Swedish government forced certain individuals to be sterilized as part of a “scientific and modern way of changing society for the better,” according to one historian. At first, only mentally ill people were sterilized, but poor, single mothers were later included. Revelation of the Nazi atrocities did not halt eugenics in Sweden, but the women’s movement in the 1970s pushed for an end to forced sterilizations.

In 1994, China passed the Maternal and Infant Health Care Law, which proposes “ensuring the quality of the newborn population” and forbids procreation between two people if physical exams show “genetic disease of a serious nature . . . that may totally or partially deprive the victim of the ability to live independently, that [is] highly

possible to recur in generations to come, and that [is] medically considered inappropriate for reproduction.” Such “genetic diseases” include mental retardation, mental illness, and seizures, conditions that are ill-defined in the law and are not necessarily inherited.

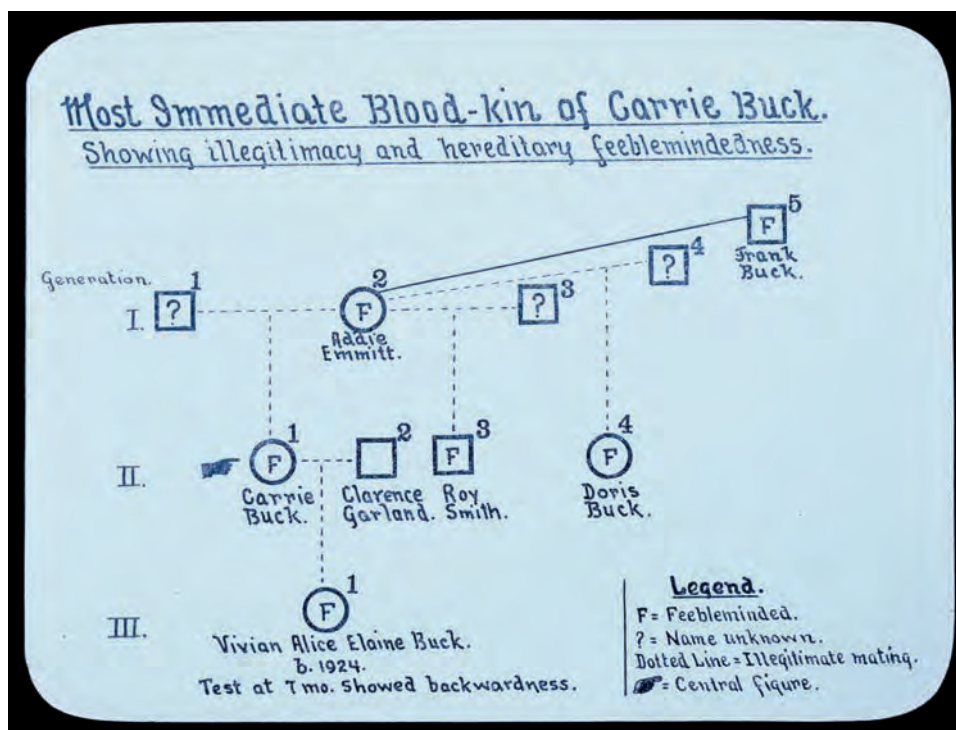
The Dor Yeshorim program in the orthodox Jewish community in New York City, described in chapter 15, may be considered eugenics. Founded in the early 1980s by a rabbi who had lost four children to Tay-Sachs disease, the program confidentially identifies carriers of genetic diseases in Ashkenazi populations. People use the information to prevent reproduction between certain individuals, but the goal is to prevent suffering, not to improve society.

Population genetic “biobanks,” described in chapter 14, acquire genetic information on their citizens. These projects are not eugenic, however, because the information is used to improve health, not to make reproductive decisions. Eugenics, in contrast, uses such information to maximize the genetic contribution from those

deemed desirable and minimize the contribution from those considered unacceptable. A major fallacy of eugenics is its subjectivity. Who decides which traits are desirable or superior?

Because genetic technologies may affect reproductive choices and can influence which alleles are passed to the next generation, modern genetics has sometimes been compared to eugenics. Medical genetics and eugenics differ in their overall goals. Eugenics aims to skew allele frequencies in future generations by allowing only people with certain “valuable” genotypes to reproduce, for the supposed benefit of the population as a whole. The goal of medical genetics, in contrast, is usually to skew allele frequencies in order to prevent suffering on a family level.

One particularly frightening aspect of the eugenics movement early in the twentieth century was the vague nature of the traits considered hereditary and undesirable, such as “feeble-mindedness.” Now, as human genomes are analyzed and compared, will eugenics resurge? Will we use new genetic information to choose the traits of the next generation? Many people fear that tests to identify carriers or disease susceptibility will be used eugenically, particularly in nations where the government does not underwrite health care. Laws are being implemented in many nations to prevent genetic discrimination. Let’s hope that in addition to deciphering our genetic blueprints, we also learn how to apply that information wisely. Unlike other species, we have the ability to affect our own evolution.



**Figure 16.23** Eugenics sought to abolish “feeble-mindedness.” In 1927, 17-year-old Carrie Buck, of Charlottesville, stood trial for the crime of having a mother who lived in an asylum for the feeble-minded, and having a daughter out-of-wedlock (following rape) also deemed feeble-minded, as was Carrie herself, though she was a B student in school. Ruled Sir Oliver Wendell Holmes, Jr., “three generations of imbeciles are enough.” Carrie Buck made history as the first person to be sterilized to prevent having another “socially inadequate offspring.”

## Key Concepts

1. Eugenics is the control of individual human reproduction for societal goals, maximizing the genetic contribution of those deemed acceptable (positive eugenics) and minimizing the contribution from those considered unacceptable (negative eugenics).
2. Some people consider modern genetic screening practices eugenic, but genetic testing usually aims to prevent or alleviate human suffering.



# Summary

## 16.1 Human Origins

1. The first primates were rodentlike insectivores that lived about 60 million years ago. By 30 to 40 million years ago, monkeylike *Aegyptopithecus* lived. **Hominoids**, ancestral to apes and humans, lived 22 to 32 million years ago. They include *Dryopithecus* and other primates who began to walk upright.
2. **Hominins**, ancestral to humans only, appeared about 19 million years ago. They were more upright, dwelled on the plains, and had smaller brains than their ancestors.
3. At least three types of hominins lived about 6 million years ago, shortly after the split from the chimp lineage.
4. The australopithecines preceded and then coexisted with *Homo habilis*, who lived in caves, had strong family units, and used tools extensively. *Homo erectus* was a contemporary who outsurvived *H. habilis*, lived in societies, and used fire. *Homo sapiens idaltu* lived about 156,000 years ago, and looked like us.
5. Neanderthals were a dead end whose split from the human lineage happened about 516,000 years ago. Modern humans appeared about 40,000 years ago, and culture was apparent by 14,000 years ago.

## 16.2 Molecular Evolution

6. Molecular evolution considers differences at the genome, chromosome, protein, or

DNA sequence levels with mutation rates to estimate species relatedness.

7. Targeted comparative sequencing aligns corresponding DNA sequences in different species to reveal evolutionary relatedness.
8. Humans and chimps share 98.7 percent of their protein-encoding gene sequences. Indels, introns, and repeats create genome differences between humans and chimps.
9. Single genes and differences in gene expression can account for great distinctions between chimps and humans.
10. The human genome shows many signs of past duplication.
11. Amplifying ancient DNA is difficult because contamination may occur.
12. Closely related species have similar chromosome banding patterns. Genes in the same order on chromosomes in different species are **syntenic**.
13. A highly conserved gene or protein is one in which the DNA sequence is similar or identical in different species, and presumably indicates importance.

## 16.3 Molecular Clocks

14. Gene sequence information from several species may be used to construct evolutionary tree diagrams, and a molecular clock based on the known mutation rate of the gene applied.

Different genes mutate at different rates. Molecular trees indicate when species diverged from shared ancestors.

15. Parsimony analysis selects the evolutionary trees requiring the fewest mutations, which are therefore the most likely.
16. Molecular clocks based on mtDNA date recent events through the maternal line because this DNA mutates faster than nuclear DNA. Y chromosome genes trace paternal lineage. Both types of evidence are used to study human origins and expansions.

## 16.4 Eugenics

17. **Eugenics** is the control of individual reproduction to serve a societal goal.
18. Positive eugenics encourages those deemed acceptable or superior to reproduce. Negative eugenics restricts reproduction of those considered inferior. Eugenics extends the concept of natural selection and Mendel's laws but does not translate well into practice.
19. Some aspects of genetic technology affect reproductive choices and allele frequencies, but the goal is to alleviate or prevent suffering, not to change society.

# Review Questions

1. Arrange the following primates in the order in which they lived, indicating any that may have overlapped in time.
  - a. *Homo erectus*
  - b. *Australopithecus anamensis*
  - c. *Dryopithecus*
  - d. Neanderthals
  - e. *Ardipithecus*
  - f. *Homo habilis*
  - g. *Australopithecus garhi*
  - h. *Homo sapiens idaltu*
2. What is the difference between a hominoid and a hominin?
3. Some anthropologists classify chimpanzees along with humans in genus *Homo*. How does this conflict with fossil evidence of the *Australopithecus* species? With DNA sequence evidence from Neanderthals?
4. Give an example of how a single gene difference can have a profound effect on the phenotypes of two species.
5. What is the evidence that *Australopithecus garhi* may have been a direct ancestor of *Homo*?
6. Give an example of molecular evidence that is consistent with fossil or other evidence.
7. Describe the type of information that Y chromosome and mitochondrial DNA sequences provide.
8. List three aspects of development, anatomy, or physiology that were important in human evolution.
9. Why is a DNA sequence that is highly conserved among humans and chimps, gorillas, and orangutans unlikely to vary greatly among human populations?
10. Explain how indels could cause the divergence of our genome sequence from that of chimpanzees, yet not contribute to observable differences between the two species.

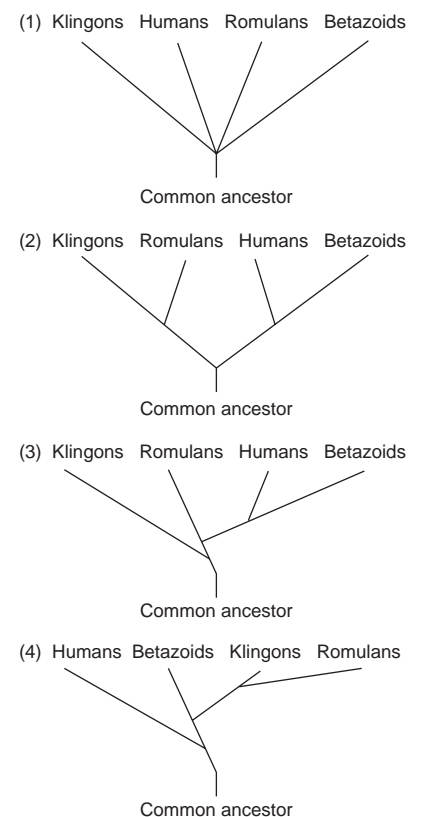
11. Protein-encoding genes have different mutation rates. How might this complicate the interpretation of targeted comparative sequencing experiments?
12. Cite two ways that humans and chimps can differ greatly at the genetic level, but still be very alike in terms of DNA sequence.
13. Why does comparing gene sequences offer more information for molecular evolution studies than comparing protein sequences?
14. Why can comparing the sequences of different genes or proteins lead to different conclusions about when two groups diverged from a common ancestor?
15. Why is comparing the DNA sequence of one gene a less accurate estimate of the evolutionary relationship between two species than a DNA hybridization experiment that compares large portions of the two genomes?
16. Cite a limitation of comparing chromosome banding patterns to estimate species' relationships.
17. What types of information are needed to construct an evolutionary tree diagram? What assumptions are necessary? What are the limitations of these diagrams?
18. Researchers compare a number of types of information in the human and chimp genomes, including SNPs, indels, and linkage patterns (haplotypes), discussed in this and other chapters. Define each of these types of information.
19. How can the human and chimp genomes be nearly 99 percent alike in DNA sequence, yet still be different?
20. Give an example of how a single gene change can influence evolution.
21. Cite three examples of eugenic actions or policies.
22. Distinguish between positive and negative selection, and between positive and negative eugenics. How do selection and eugenics differ?

## Applied Questions

1. Select an example from this chapter and explain how it illustrates one of the forces of evolutionary change discussed in chapter 15 (natural selection, nonrandom mating, migration, genetic drift, or mutation.)
2. Describe a scenario of how a group of australopithecines might have branched off into *Homo*.
3. Suggest an explanation for why there were many species of *Australopithecus* living at one time, but only one of *Homo* living today.
4. A geneticist aboard a federation starship is given the task of determining how closely related Humans, Klingons, Romulans, and Betazoids are. Each organism walks on two legs, lives in complex societies, uses tools and technologies, looks similar, and reproduces in the same manner. Each can interbreed with any of the others. The geneticist finds the following data:
  - Klingons and Romulans each have 44 chromosomes. Humans and Betazoids have 46 chromosomes. Human chromosomes 15 and 17 resemble part of the same large chromosome in Klingons and Romulans.
  - Humans and Klingons have 97 percent of their chromosome bands in common. Humans and Romulans have 98 percent of their

chromosome bands in common, and Humans and Betazoids show 100 percent correspondence. Humans and Betazoids differ only by an extra segment on chromosome 11, which appears to be a duplication.

- The cytochrome *c* amino acid sequence is identical in Humans and Betazoids, differs by one amino acid between Humans and Romulans, and differs by two amino acids between Humans and Klingons.
  - The gene for collagen contains 50 introns in Humans, 50 introns in Betazoids, 62 introns in Romulans, and 74 introns in Klingons.
  - Mitochondrial DNA analysis reveals many more individual differences between Klingons and Romulans than between Humans and Betazoids.
- a. Hypothesize the chromosomal aberrations that might explain the karyotypic differences among these four types of organisms.
  - b. Which are our closest relatives among the Klingons, Romulans, and Betazoids? What is the evidence for this?
  - c. Are Klingons, Romulans, Humans, and Betazoids distinct species? What information reveals this?
  - d. Which of the evolutionary tree diagrams is consistent with the data?



5. Contrary to popular wisdom, evolution does not strive toward perfection. How does the ability of humans to taste and smell illustrate this point?
6. Why might it be important to identify DNA sequences that chimps have that

- humans do not, as well as identify sequences unique to humans?
- A molecular anthropologist who is studying diabetes in native Americans feels that he can obtain information on why certain groups are prone to the disorder by analyzing genetic variants in small, isolated populations around the world. Do you think that the goal of understanding disease and alleviating suffering in one group of people justifies obtaining and studying the DNA of other people who have had little contact with cultures outside their own? Can you suggest a compromise intervention?
  - In 1997, law schools in two states reversed their affirmative action policies and began evaluating all applicants on an equal basis—that is, applying the same admittance requirements to all. In fall 1997, classrooms of new law students had few, if any, nonwhite faces. How was this action eugenic, and how was it not?
  - Several women have offered to be inseminated with sperm from the Ice Man, who died 5,300 years ago in the Alps. If sperm could have been recovered, and a woman inseminated, what do you think the child would be like?
  - Locate a disease-causing gene on a human chromosome, and consult figure 16.16 to determine where it may have a counterpart in the horse genome.

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study**, chapter 16, and **Web Activities** to find the website links needed to complete the following activities.

- Go to the website for the National Institutes of Health Intramural Sequencing Center. Under Scientific Projects, click Comparative Vertebrate Sequencing (first choice). Scroll down. Locate one where the red bars align for humans and chimps and/or another species. Read “gene name” at the bottom of the screen, and then look up this name on OMIM. Describe a human trait or condition that this gene confers.
- Go to the Image Archive on the American Eugenics Movement website. Look at several images, and either find one that presents a genetic disorder and describe it, or find an image that presents biologically incorrect information, and explain the error.

- Several websites promise to consult your Y chromosome or mitochondrial DNA and tell you where you came from. Some researchers have cautioned that these companies make false promises. Look at some of these websites, and identify limitations to the technologies used or vague language used to disguise the fact that results may not be very specific.

### Case Studies and Research Results

- In The Netherlands, the proposed Groningen Protocol presents guidelines for euthanasia of newborns who suffer from untreatable pain, or extreme deformities, or who require continual life support. The guidelines specifically mention disorders with genetic components, such as severe spina bifida and epidermolysis bullosa, which blisters the skin.

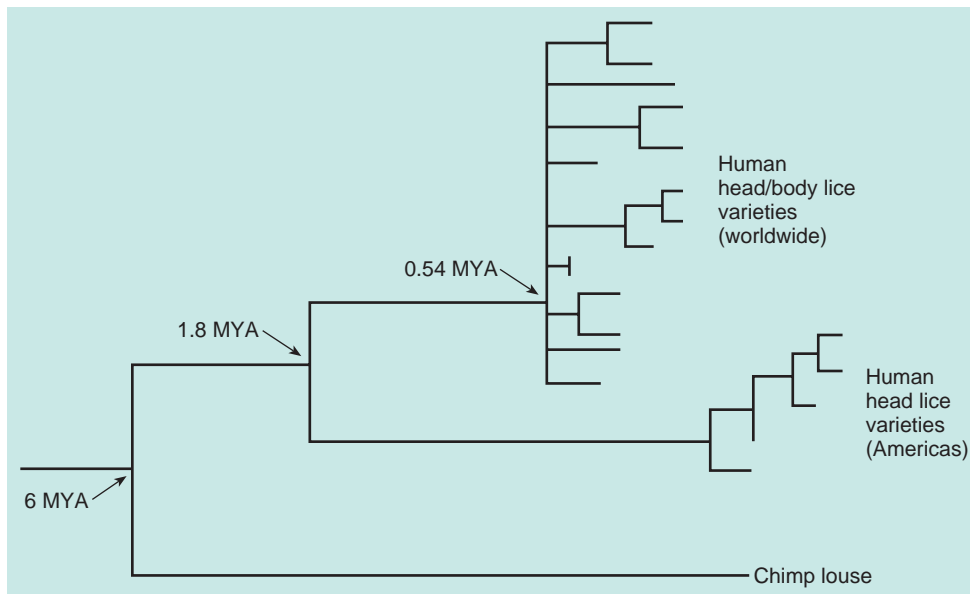
Do you agree or disagree with the following justifications for newborn euthanasia? Cite reasons for your answers.

- Approving guidelines is a formality—hastening the death of a severely ill newborn is already practiced, and not only in The Netherlands.
  - Having a government-sanctioned protocol will prevent abuse.
  - The intent is to relieve suffering, and the procedure requires parental consent.
  - Only 10 or fewer newborns will likely be euthanized in the country each year, out of a total population of 16 million.
  - The euthanized infants would never have contributed genes to the next generation.
  - The practice will be restricted to what the government considers hopeless cases.
- Consider the following brain sizes:

Animal	Brain volume (cubic centimeters)
<i>Homo sapiens sapiens</i> (us)	1400–1500
<i>Homo sapiens idaltu</i>	1450
<i>Homo erectus</i>	1000–1250
<i>Australopithecus</i>	380
Chimpanzee	350–380
<i>Homo floresiensis</i>	380
Gorilla	350–450

- Explain how these data either support or refute the hypothesis that increasing brain size correlates to increased intelligence.
  - Explain a limitation of the ways in which we learn about our ancestors or relatives that might account for confusing results when we compare traits.
- Austrian researchers discovered at an ancient burial site in the eastern part of their nation remains of two newborns, their preserved skeletons facing each other in a fetal position. The bones were small and thin, the heads small. The remains were covered with red clay, in which ornaments were embedded.
    - What was the likely species of the newborns?
    - Describe two other types of information that might explain a little about the culture of the hominins represented in the remains.
  - A magazine article featured parents who filed a “wrongful birth” lawsuit against their doctor for failing to offer prenatal testing for spina bifida, which their daughter was born with in 2003—even though they love the child dearly. They will not say whether they would have ended the pregnancy had they known about the birth defect. If they had ended it, would that have been a eugenic act? Explain your answer.
  - For more than 20 million years, lice have lived on the skins of primates. Researchers compared a 1,525-base-pair sequence of mtDNA among modern varieties of lice, and, applying the mutation rate, derived the evolutionary tree on the next page. It depicts a split in the louse lineage, with one group of head and body lice living throughout the world, and another group of only head lice living in the Americas.
    - What events in human evolution roughly correspond to the branch points in the louse evolutionary tree?
    - What might be the significance of the similarity between the evolutionary trees for lice and humans?
    - The researchers interpreted their findings to possibly indicate that lice were transferred from archaic humans to modern humans. What is the evidence for this hypothesis? What other types of evidence or background information might make it more convincing?
    - What is a limitation of this research?





19. In the 1870s, prison inspector and self-described sociologist Richard Dugdale noticed that many inmates at his facility in Ulster County, New York, were related. He began studying them, calling the family the “Jukes,” although he kept records of their real names. Dugdale traced the family back seven generations to a son of Dutch settlers, named Max, who was a pioneer and lived off the land. Margaret, “the mother of criminals,” as Dugdale would write in his 1877 book *The Jukes: A Study in Crime, Pauperism, Disease and Heredity*, married one of Max’s sons, and the couple presumably ultimately gave rise to 540 of the 709 criminals on Dugdale’s watch. Dugdale attributed the Jukes’ less desirable characteristics to heredity.

The Jukes study influenced social scientists to probe other families seem-

ingly riddled with misfits—they were all caucasian, descended from colonial settlers, and poor. Poverty was not seen as an economic problem, but as a reflection of inborn degeneracy, that if left unchecked would cost society greatly. Dugdale’s book fed the fledgling eugenics movement. In 1911, researchers at the Eugenics Record Office in Cold Spring Harbor described the Jukes’ phenotype as “feeble-mindedness, indolence, licentiousness, and dishonesty.” The Jukes story and others were used to support compulsory sterilization of those deemed unfit. But the original research on the Jukes family was flawed, and its accuracy never questioned. Less notorious Jukes family members served in respected professions, some even holding public office. The Jukes were vindicated in 2003, when archives at the State University of

New York at Albany revealed the original names of the people in Dugdale’s account; most were not even related. The Jukes family curse was more legend than fact.

- What would have had to happen to the original jailed Jukes family members or their descendants to be considered eugenic?
- How could studies on one family harm others?
- Cite an example of an idea based on eugenics today or in the recent past.
- If you were a contemporary of Dugdale’s, what type of evidence would you have sought to counter his ideas?

20. A Y chromosome haplotype consists of specific mutations for the *SRY* gene and genes called *M96* and *P29*. Among modern Africans, there are three variants of this haplotype. Two of them are found only among Africans, but the third variant of the Y haplotype, called E3, is also seen in western Asia and in parts of Europe. Researchers examined specific subhaplotypes (variations of the variations) and found that one type, called E-M81, accounts for 80 percent of the Y chromosomes sampled in northwest Africa, diminishing sharply in incidence to the east, and not present in sub-Saharan Africa at all. That same haplotype is found in a small but significant percentage of the Y chromosomes in Spain and Portugal. Consult a map, and propose a scenario for this gene flow. What further information would be useful in reconstructing migration patterns?

## A Second Look

- Give two examples of hominins that overlapped in time.
- How might you use mtDNA or Y chromosome haplotypes on fossils of the hobbits to trace their origin?
- Does the existence of the Hobbits argue for the replacement hypothesis or the multiregional hypothesis?

Learn to apply the skills of a genetic counselor with this additional case found in the *Case Workbook in Human Genetics*:

Novelty seeking and ADHD



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.



# Genetics of Immunity

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  - Genetic Control of Immunity
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- 17.2 **The Human Immune System**
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## GENE EXPRESSION IN RHEUMATOID ARTHRITIS

Imagine not being able to hold a pen, or turn a door-knob. For someone with rheumatoid arthritis (RA), simple tasks become impossible. The joints become chronically inflamed, causing painful “flares”. Great deformity results.

RA has been considered a classic autoimmune disease, in which the immune system attacks the tissues. It isn’t inherited—RA does not follow a Mendelian pattern in families, and is not more likely to occur in both members of MZ (identical) twins compared to both members of DZ (fraternal) twins. However, MZ twins in whom one has RA and the other doesn’t provide a way to investigate the non-genetic factors that contribute to the disease.

Researchers withdrew fluid from the joints of eleven pairs of MZ twins in whom one had RA and the other didn’t. They extracted DNA from cells in the fluid and applied it to DNA microarrays that detected expression (mRNA production) of 20,000 genes. Three genes were greatly overexpressed in the twins who had RA, and the corresponding proteins were overabundant in their joint fluid. All three proteins had never been associated with RA, but they made sense. One destroys bone and cartilage. Another deactivates the hormone cortisol, whose levels are diminished in RA. The third protein stimulates blood vessel formation, which enhances inflammation. Researchers are developing drugs that target the three proteins, and investigating environmental influences that may have triggered RA in one identical twin but not the other.



Rheumatoid arthritis causes great deformity of the hands and very painful joints. It isn’t inherited, but is associated with altered expression of certain genes.



## 17.1 The Importance of Cell Surfaces

We share the planet with plants, microbes, fungi, and other animals. The human immune system has evolved in a way that keeps potentially harmful organisms out of our bodies. This system is a mobile army of about 2 trillion cells, the biochemicals they produce, and the organs where they are produced and stored. Protection is based upon the ability of the immune system to recognize “foreign” or “nonself” surfaces, which include those of microorganisms such as bacteria and yeast; nonliving “infectious agents” such as viruses; and even tumor cells and transplanted cells. Then, the immune system carries out a highly coordinated attack that includes both general and highly specific responses.

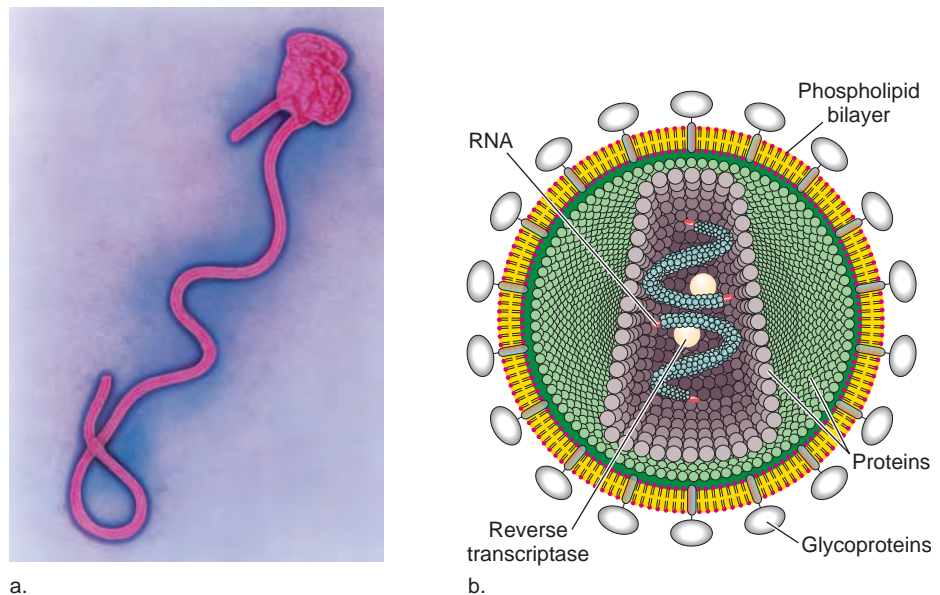
### Pathogens

Pathogens are organisms or infectious agents that cause disease. Pathogenic organisms include bacteria and single-celled eukaryotes such as paramecia and amoebae. Infectious agents include viruses and prions. Bacteria are prokaryotic cells, which means that they lack membrane-bounded, complex organelles (figure 17.1). Antibiotic drugs treat bacterial infections. Much of the action of the immune system is directed against viruses, which are much simpler than cells and straddle the boundary between the nonliving and the living. Few drugs can treat viral infections.

A **virus** is a single or double strand of RNA or DNA wrapped in a protein coat, and in some types, in an outer envelope, too. A virus can reproduce only if it enters and uses a host cell’s energy resources, protein synthetic machinery, and secretion pathway. It is a stunningly streamlined structure. A virus may have only a few protein-encoding genes, but many copies of the same protein can assemble to form an intricate covering, like the panes of glass in a greenhouse. Ebola virus, for example, has only seven types of proteins, but they assemble into a structure capable of reducing a human body to little more than a bag of blood and decomposed tissue (figure 17.2a). In contrast, the



**Figure 17.1 Bacterial pathogens.** (a) *Escherichia coli* is a normal resident of the human small intestine, but under certain conditions can produce a toxin that causes severe diarrhea (“food poisoning”) and can damage the kidneys. (b) *Streptococcus pyogenes* causes several types of skin infections, including cellulitis and impetigo, as well as scarlet fever and “necrotizing fasciitis,” also known as a “flesh-eating” infection. (c) *Bacillus anthracis* causes anthrax, which affects the skin or the lungs.



**Figure 17.2 Viral pathogens.** Viruses are nucleic acids in protein coats. (a) Ebola virus is a single strand of RNA and seven proteins. People become infected when they touch body fluids of the infected. (b) HIV consists of RNA surrounded by several protein layers. Once inside a human cell, the virus uses a viral enzyme, reverse transcriptase, to make a DNA copy of its RNA. The virus then inserts this copy into the host cell’s DNA. Before the infected cell dies, it produces and releases many viral particles.

smallpox virus has more than 100 different types of proteins, and HIV is also complex (figure 17.2b).

Viruses are with us all the time—not only when we are ill. Part of the DNA sequence of some human chromosomes includes viral DNA sequences that are vestiges of past infections, perhaps passed,

silently, from distant ancestors. Many DNA viruses reproduce by inserting their DNA into the host cell’s DNA. In contrast, it takes several steps for an RNA virus to insert DNA into a human chromosome because the RNA must first be copied into DNA by a viral enzyme called reverse transcriptase. The DNA that represents the

RNA virus then inserts into the host cell's chromosome. (In some viruses, the invading DNA is replicated separately from a host chromosome.) Certain RNA viruses are called retroviruses because they transmit genetic information opposite the usual direction—that is, instead of transmitting information from DNA to RNA to protein, viral RNA is copied into DNA, which may then be copied back into RNA to guide the synthesis of viral proteins. HIV is a retrovirus.

Once viral DNA integrates into the host cell's DNA, it can either remain and replicate along with the host's DNA without causing harm, or it can take over and kill the cell. Activated viral genes direct the host cell to replicate viral DNA and then use it to manufacture viral proteins, at the expense of the cell's normal activities. The infected cell fills with viral DNA and protein, which assemble into new viruses. The cell bursts, releasing many new virus copies into the body.

Diverse viruses infect all types of organisms. They were discovered in tobacco plants, but they also infect microorganisms, fungi, and, of course, animals. Their genetic material cannot repair itself, so the mutation rate may be high—which is one reason why we cannot develop an effective vaccine against HIV or the common cold, and why new influenza vaccines must be developed each year. Prions are interesting because they cause infectious disease that the immune system cannot fight. Recall from chapter 10 that prions are infectious proteins. The immune system does not recognize infectious prions because they are variants of proteins normally in the body that have the same amino acid sequence. They differ from harmless prion protein in their three-dimensional structure.

## Genetic Control of Immunity

Genes that affect immunity may confer susceptibilities or resistances to certain infectious diseases, or raise the risk of developing an allergic or **autoimmune** condition, in which the immune system attacks an individual's own tissues. Most such effects are polygenic. For example,

systemic lupus erythematosus is an autoimmune disorder associated with inheriting certain alleles of dozens of genes.

A few types of single genes exert powerful effects on immunity. Certain classes of genes oversee immunity by encoding **antibodies** and **cytokines**, which are proteins that directly attack foreign antigens. An **antigen** is any molecule that can elicit an immune response. The antigens on a person's cells can evoke an immune response in another individual such as in a transplant recipient. That is, an organ donor's "self" antigens may be "nonself" to the recipient. Antigens are proteins or carbohydrates. Genes specify the cell surface antigens that mark the body's cells as "self." They do this directly by encoding antigen proteins, or by encoding enzymes required to synthesize particular carbohydrates that are antigens.

Because genes control immunity, mutations can impair immune function, causing immune deficiencies, autoimmune disorders, allergies, and cancer. Understanding how genes control immunity makes it possible to enhance or redirect the system's ability to fight disease. We begin our look at the genetics of normal immunity with some familiar examples of our personal cellular landscapes.

## Blood Groups

Transplanting an organ as complex as a liver is risky. A far simpler type of transplant, although still very dependent on matching cell surfaces, is a blood transfusion. Using one person's blood to restore another's health was proposed centuries ago. To do so safely and successfully, however, it was necessary to understand the genetics of blood types.

### ABO Blood Groups

The first transfusions, performed in the late 1600s, used lamb's blood. By the 1800s, physicians were trying to use human blood. Results were unpredictable—some recipients recovered, but others died. So poor was the success rate that, by the late 1800s, many nations banned transfusions.

Then Austrian physician Karl Landsteiner began investigating why transfusions sometimes worked and sometimes didn't. In 1901, he determined that human blood was

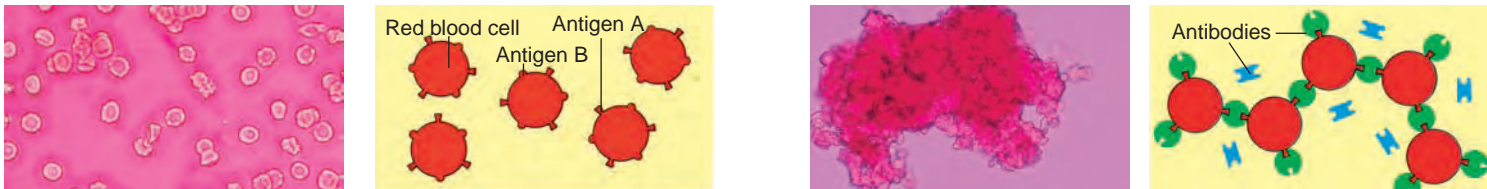
of differing types, and only certain combinations were compatible. Specifically, he identified three types of blood that he called A, B, and O, and found that transfusing between types often led to disaster. In 1902, other researchers discovered the rare type AB. In 1910, identification of the ABO blood antigen locus (OMIM 110300) explained these four blood types and their incompatibilities (**figure 17.3**). Today we know of 26 blood group systems that include nearly 200 antigens.

Recall from chapter 5 that the *I* gene alleles encode enzymes that place antigens A, B, both A and B, or neither antigen on sugar chains on red blood cells (see table 5.1). Blood type incompatibility occurs when a person's immune system manufactures antibodies that attack the antigens his or her cells do not carry. A person with blood type A, for example, has antibodies against type B antigen. If he or she is transfused with type B blood, the anti-B antibodies clump the transfused red blood cells, blocking circulation and depriving tissues of oxygen. A person with type AB blood doesn't manufacture antibodies against either antigen A or B, because if he or she did, the person's own blood would clump. Therefore, someone with type AB blood can receive any ABO blood type. Type O blood has neither A nor B antigens, so it cannot stimulate an immune response in a transfusion recipient; people with type O blood can therefore donate to anyone. However, the idea that a person with AB blood is a "universal recipient" and one with type O blood is a "universal donor" is more theoretical than practical, because antibodies to other donor blood antigens (for example, the Rh factor, discussed next) can cause slight incompatibilities. For this reason, blood is as closely matched as possible.

A person who receives mismatched blood quickly feels the effects—anxiety, difficulty breathing, facial flushing, headache, and severe pain in the neck, chest, and lower back. Red blood cells burst, releasing free hemoglobin that can damage the kidneys.

### The Rh Factor

ABO blood type is often further differentiated by a + or –, which refers to another blood group antigen called the Rh factor (OMIM 111700). A person is Rh<sup>+</sup> if red blood cells have a surface molecule called



Compatible Blood Types (no clumping)

Donor	Recipient
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

Incompatible Blood Types (clumping)

Donor	Recipient
A	B, O
B	A, O
AB	A, B, O

**Figure 17.3 ABO blood types.** Genetics explains blood incompatibilities.

the RhD antigen. Several less common Rh antigens can also confer the Rh<sup>+</sup> blood type. The Rh antigens were originally identified in rhesus monkeys, hence the name.

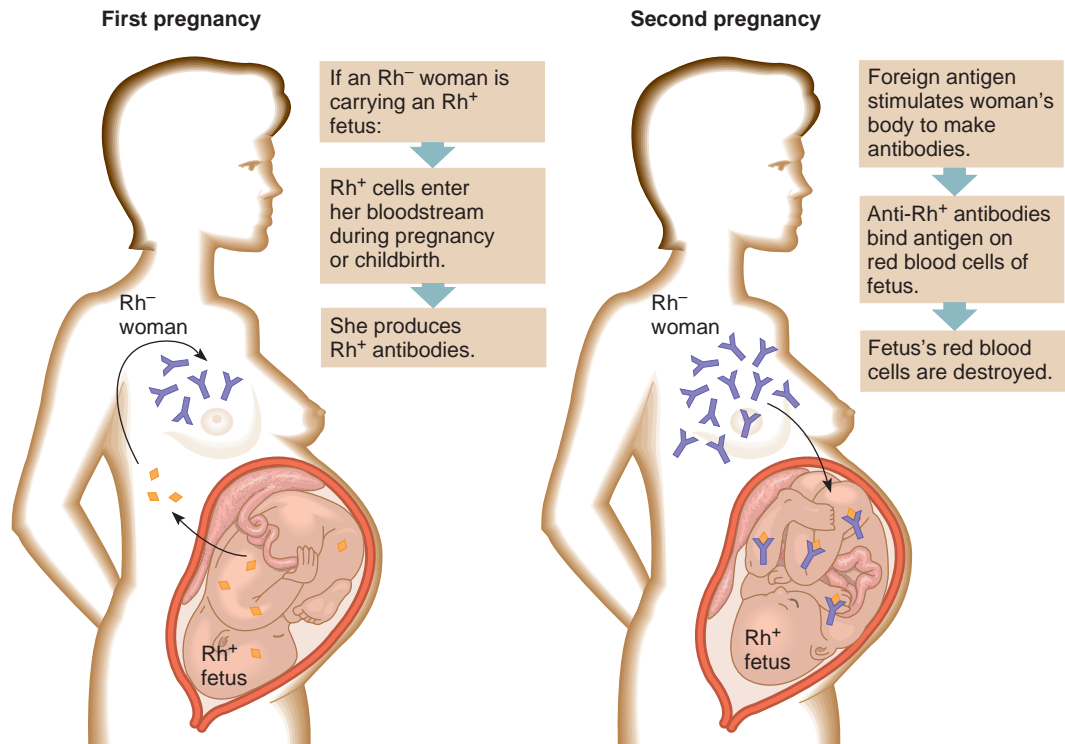
Rh type is important when an Rh<sup>+</sup> man and an Rh<sup>-</sup> woman conceive a child who is Rh<sup>+</sup>. The pregnant woman's immune system reacts to the few fetal cells that enter her bloodstream by manufacturing antibodies against them (**figure 17.4**). Not enough antibodies form to harm the first fetus, but if she carries a second Rh<sup>+</sup> fetus, the woman's now plentiful antibodies attack the fetal blood supply. In the fetus, bilirubin, a breakdown product of red blood cells, accumulates, damaging the brain and turning the skin and whites of the eyes yellow. The fetal liver and spleen swell as they rapidly produce new red blood cells. If the fetus or newborn does not receive an "exchange" transfusion of Rh<sup>-</sup> blood and have some of its Rh<sup>+</sup> blood removed, then the heart and blood vessels collapse and fatal respiratory distress sets in. Rh disease that progresses this far is called hemolytic disease of the fetus and newborn.

Fortunately, natural and medical protections make this condition rare today, although exchange blood transfusions were once common. Determining parental ABO blood types indicates whether an immune reaction against the fetus of an Rh-incompatible couple will take place. If the woman has type O blood and the fetus is A or B, then her

anti-A or anti-B antibodies attack the fetal blood cells in her circulation before her immune system has a chance to manufacture the anti-Rh antibodies. This blocks the anti-Rh reaction.

Determining a pregnant woman's blood type, including Rh type, is part of routine prenatal care. If there is an Rh incompatibility, injection of a substance called RhoGAM during each pregnancy and after each birth

covers antigens on fetal blood cells in the woman's circulation so that she does not manufacture anti-Rh antibodies. RhoGAM is actually antibody against the Rh antigen. However, events other than pregnancy and childbirth can expose an Rh<sup>-</sup> woman's system to Rh<sup>+</sup> cells, placing even her first fetus at risk. These include amniocentesis, a blood transfusion, an ectopic (tubal) pregnancy, a miscarriage, or an abortion.



**Figure 17.4 Rh incompatibility.** Fetal cells entering the pregnant woman's bloodstream can stimulate her immune system to make anti-Rh antibodies, if the fetus is Rh<sup>+</sup> and she is Rh<sup>-</sup>. A drug called RhoGAM prevents attacks on subsequent fetuses.



## Other Blood Groups

The second blood group discovered, in 1927, was the MN system; a third allele, S, was identified 20 years later. The three alleles are codominant, combining to form six different genotypes and phenotypes. The MNS antigens bind to two specific glycoproteins on red blood cell surfaces.

Another blood-type determining gene is called Lewis (OMIM 111100). It encodes an enzyme, fucosyltransferase (FUT3), that adds an antigen to the sugar fucose, which the product of the *H* gene then places on red blood cells. (Recall from section 5.1 that the *H* gene is necessary for ABO expression.) Individuals with genotype *LeLe* or *Lele* have the Lewis antigen on red blood cell plasma membranes and in saliva, whereas *lele* people do not produce the antigen. Another interesting gene that affects the blood is the secretor gene (FUT2, OMIM 182100). People who have the dominant allele *Se* secrete the A, B, and H antigens in body fluids, including semen, saliva, tears, and mucus.

Cell surfaces are dotted with many molecules other than those that confer blood types. Many of these protein surface features are encoded by genes that are part of a 6-million-base-long cluster on the short arm of chromosome 6 called the **major**

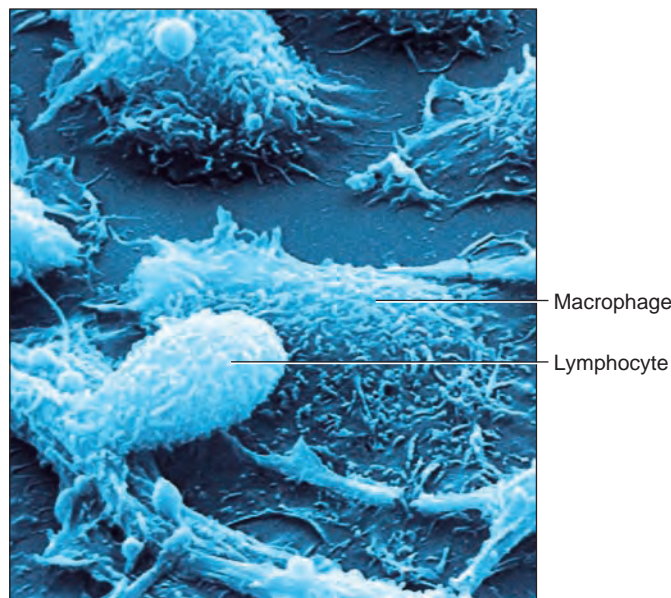
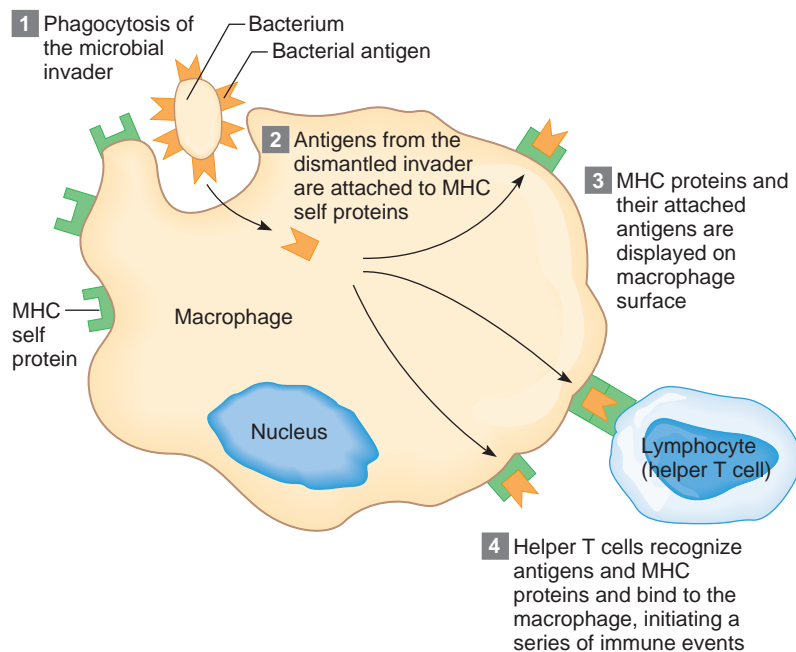
**histocompatibility complex (MHC)**. The MHC includes about 70 genes.

## The Human Leukocyte Antigens

MHC genes are classified into three functional groups. Class III MHC genes encode proteins that are in blood plasma (the liquid portion of blood, discussed in section 11.1) and that provide nonspecific immune functions. Class I and II genes of the MHC encode the **human leukocyte antigens (HLA)**, first studied in leukocytes (white blood cells). The HLA proteins link to sugars, forming branchlike glycoproteins that extend from cell surfaces. Some HLA glycoproteins latch onto bacterial and viral proteins, displaying them like badges to alert other immune system cells. This action, called antigen processing, is often the first step in an immune response. The cell that displays the foreign antigen is called an **antigen-presenting cell**. **Figure 17.5** shows how a large cell called a macrophage displays bacterial antigens. Certain white blood cells called T cells (or T lymphocytes) are also antigen-presenting cells. Class I and II HLA proteins differ in the types of immune system cells they alert.

All human cells with nuclei (that is, all cells except red blood cells) have some HLA antigens that identify them as “self,” or belonging to the same individual. In addition to these common HLA markers are more specific markers that distinguish particular tissue types. Class I includes three genes, *A*, *B*, and *C*, that vary greatly and are found on all cell types, and three other genes, *E*, *F*, and *G*, that are more restricted in their distribution. Class II includes three major genes whose encoded proteins are found mostly on antigen-presenting cells.

Because the HLA classes consist of several genes that have many alleles, individuals have an overall HLA “type.” Only 2 in every 20,000 unrelated people match for the six major HLA genes by chance. When transplant physicians attempt to match donor tissue to a potential recipient, they determine how alike the two individuals are at these six loci. Usually at least four of the genes must match for a transplant to have a reasonable chance of success. Before DNA profiling, HLA typing was the predominant type of blood test used in forensic and paternity cases to rule out involvement of certain individuals. However, HLA genotyping has become very complex because hundreds of alleles are now known. In addition, HLA genotype and



**Figure 17.5 Macrophages are antigen-presenting cells.** A macrophage engulfs a bacterium, then displays foreign antigens on its surface, held in place by major histocompatibility complex (MHC) self proteins. This event sets into motion many immune reactions.

disease associations differ in different populations, and many people can trace their roots back to more than one population.

About 50 percent of the genetic influence on immunity stems from HLA genes. However, a few disorders are very strongly associated with inheriting particular HLA types. This is the case for ankylosing spondylitis, which inflames and deforms vertebrae. A person with either of two particular subtypes of an HLA antigen called B27 is 100 times as likely to develop the condition as someone who lacks either form of the antigen. HLA-associated risks are not absolute. More than 90 percent of people who suffer from ankylosing spondylitis have the B27 antigen, which occurs in only 5 percent of the general population. However, 10 percent of people who have ankylosing spondylitis do *not* have the B27 antigen, and some people who have the antigen never develop the disease. **Table 17.1** lists some disorders that are much more common in people with certain HLA types.

**Table 17.1**  
**HLA-Disease Associations**

Condition	Description
Narcolepsy	Suddenly falling asleep
Ankylosing spondylitis	Inflamed and deformed vertebrae
Reiter's disease	Inflamed joints, eyes, and urinary tract
Dermatitis herpetiformia	Burning, itchy skin lesions
Psoriasis	Scaly skin lesions
Autoimmune hepatitis	Inflamed liver
Type 1 diabetes	Inability to produce insulin
Graves disease	Malfunction of thyroid gland
Celiac disease	Small intestine is damaged when gluten (in certain grains) is eaten
Myasthenia gravis	Fluctuating weakness of voluntary muscles
Rheumatoid arthritis	Severely inflamed joints
Multiple sclerosis	Degeneration of brain and spinal cord, producing weakness and poor coordination
Systemic lupus erythematosus	Facial rash, high persistent fever, destruction of heart, brain, kidneys

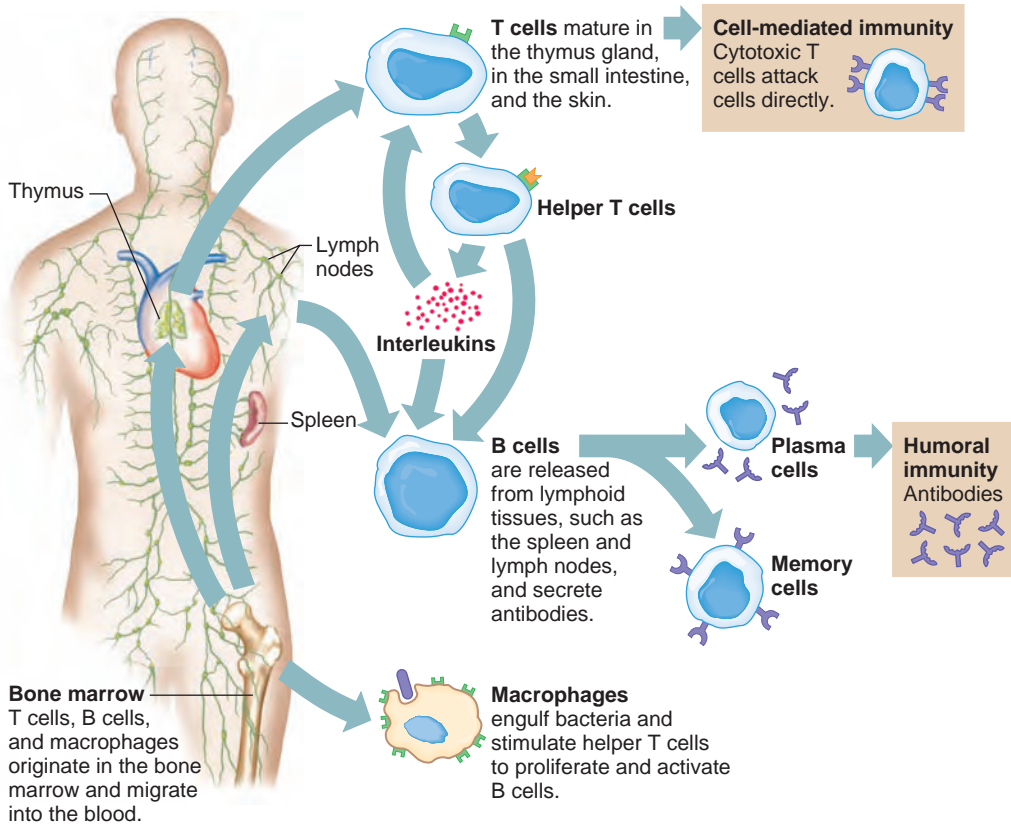
### Key Concepts

1. The immune system consists of cells and biochemicals that distinguish self from nonself antigens.
2. Pathogens include microbes and infectious agents, such as viruses, which take over a host cell's protein synthesis machinery to reproduce.
3. Blood types result from self antigen patterns on red blood cells. HLA cell surface proteins establish self and display foreign antigens.

## 17.2 The Human Immune System

The immune system is a network of vessels called lymphatics that transport lymph fluid to bean-shaped structures throughout the body called lymph nodes. The spleen and thymus gland are also part of the immune system (**figure 17.6**).

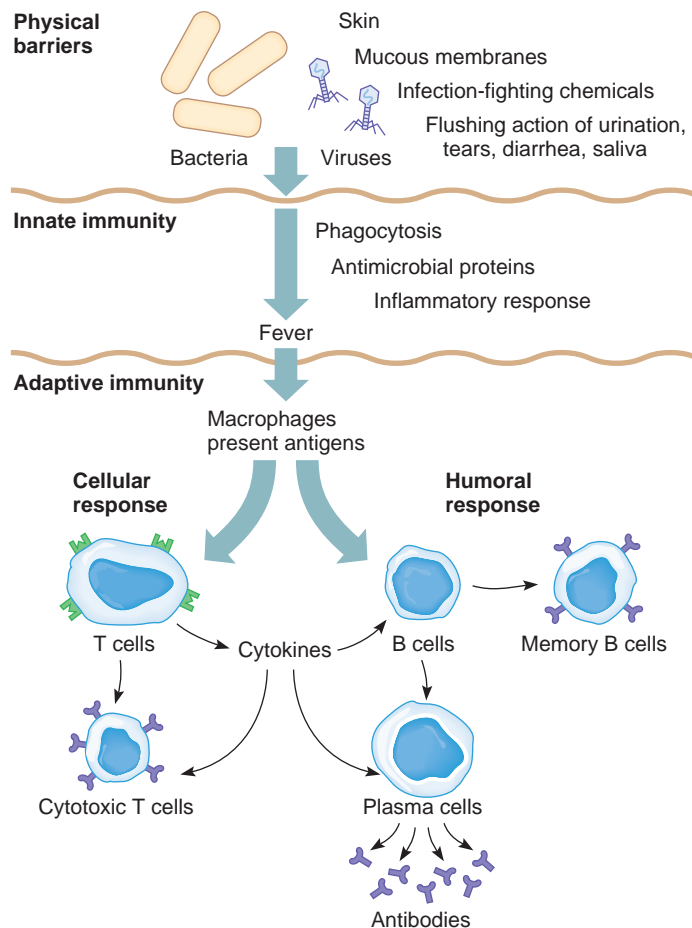
Lymph fluid carries white blood cells called lymphocytes and the wandering, scavenging macrophages that capture and degrade bacteria, viruses, and cellular debris. **B cells** and **T cells** are the two major types of lymphocytes.



**Figure 17.6 Immune cells are diverse.** T cells, B cells, and macrophages build an overall immune response. All three types of cells originate in the bone marrow and circulate in the blood.

The genetic connection to immunity is the proteins required to carry out an immune response. The immune response attacks pathogens, cancer cells,

and transplanted cells with two lines of defense—an immediate generalized **innate immunity**, and a more specific, slower **adaptive immunity**. These defenses



**Figure 17.7 Levels of immune protection.** Disease-causing organisms and viruses (pathogens) first must breach physical barriers, then nonspecific cells and molecules attack in the innate immune response. If this is ineffective, the adaptive immune response begins: Antigen-presenting cells stimulate T cells to produce cytokines, which activate B cells to divide and differentiate into plasma cells, which secrete antibodies. Once activated, these specific cells “remember” the pathogen, allowing faster responses to subsequent encounters.

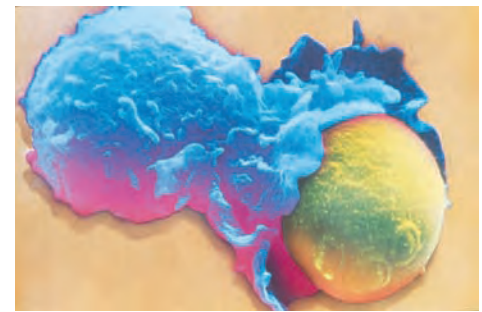
act after various physical barriers block pathogens. **Figure 17.7** summarizes the basic components of the immune system, discussed in detail in the following sections.

## Physical Barriers and the Innate Immune Response

Several familiar structures and fluids keep pathogens from entering the body in the innate immune response: unbroken skin, mucous membranes such as the lining inside the mouth, earwax, and waving cilia that push debris and pathogens up and out of the respiratory tract. Most microbes that make it to the stomach perish in a vat of churning acid—an exception is the bacterium that

causes peptic ulcers, which thrives in acid. Other microbes are flushed out in diarrhea. These physical barriers are nonspecific—that is, they keep out anything foreign, not just particular pathogens.

If a pathogen breaches these physical barriers, innate immunity provides a rapid, broad defense. The term *innate* refers to the fact that these general defenses are in the body, ready to function should infection threaten. A process called **inflammation** is a central part of the innate immune response. Inflammation creates a hostile environment for certain types of pathogens at an injury site, sending in cells that engulf and destroy them. Such cells are called phagocytes, and their engulfing action is phagocytosis (**figure 17.8**). Some white blood cell types,



**Figure 17.8 Nature's garbage collectors.** A human phagocyte engulfs a yeast cell.

such as neutrophils, are phagocytes, as are the large, wandering macrophages. Another type of white blood cell mobilized during an innate immune response is a natural killer cell, which attacks cancer and virally-infected cells without recognizing specific molecules.

During inflammation, plasma accumulates, which dilutes toxins and brings in antimicrobial chemicals. Increased blood flow with inflammation warms the area, turning it swollen and red.

Three classes of proteins participate in innate immunity—the complement system, collectins, and cytokines. Mutations in the genes that encode these proteins increase susceptibility to infection.

The **complement system** consists of plasma proteins that assist, or complement, several other defenses. Some complement proteins puncture bacterial plasma membranes, bursting the cells. Others dismantle viruses or trigger release of histamine from mast cells, another type of immune system cell that is involved in allergies. Histamine dilates blood vessels, enabling fluid to rush to the infected or injured area. Still other complement proteins attract phagocytes to an injury site.

**Collectins** are proteins that broadly protect against bacteria, yeasts, and some viruses by detecting slight differences from human cells in their surfaces. Groups of human collectins correspond to the surfaces of different pathogens, such as the distinctive sugars on yeast, the linked sugars and lipids of certain bacteria, and the surface features of some RNA viruses.

Cytokines play many roles in immunity. As part of the innate immune response, cytokines called **interferons** alert other



components of the immune system to the presence of cells infected with viruses. These cells are then destroyed, which limits the spread of infection. **Interleukins** are cytokines that cause fever, temporarily triggering a higher body temperature that directly kills some infecting bacteria and viruses. Fever also counters microbial growth indirectly, because higher body temperature reduces the iron level in the blood. Bacteria and fungi require more iron as the body temperature rises; therefore, a fever-ridden body stops their growth. Phagocytes also attack more vigorously when the temperature rises. Tumor necrosis factor is another type of cytokine that activates other protective biochemicals, destroys certain bacterial toxins, and also attacks cancer cells. Many of the aches and pains we experience from an infection are actually due to the immune response, not directly to the actions of the pathogens.

## The Adaptive Immune Response

Adaptive immunity must be stimulated into action. It may take days to respond, compared to minutes for innate immunity. Adaptive immunity is highly specific and directed.

B cells and T cells carry out adaptive immunity. In the **humoral immune response**, B cells produce antibodies in response to activation by T cells. (“Humor” means fluid; antibodies are carried in fluids.) In the **cellular immune response**, T cells produce cytokines and activate other cells. B and T cells differentiate in the bone marrow and migrate to the lymph nodes, spleen, and thymus gland, as well as circulate in the blood and tissue fluid.

The adaptive arm of the immune system has three basic characteristics. It is *diverse*, vanquishing many types of pathogens. It is *specific*, distinguishing the cells and molecules that cause disease from those that are harmless. The immune system also *remembers*, responding faster to a subsequent encounter with a foreign antigen than it did the first time. The first assault initiates a primary immune response. The second assault, based on the system’s “memory,” is a secondary immune response. This is why we get some infections, such as chickenpox, only once. However, upper respiratory infections and influenza recur because the causative viruses mutate, presenting a different face to our

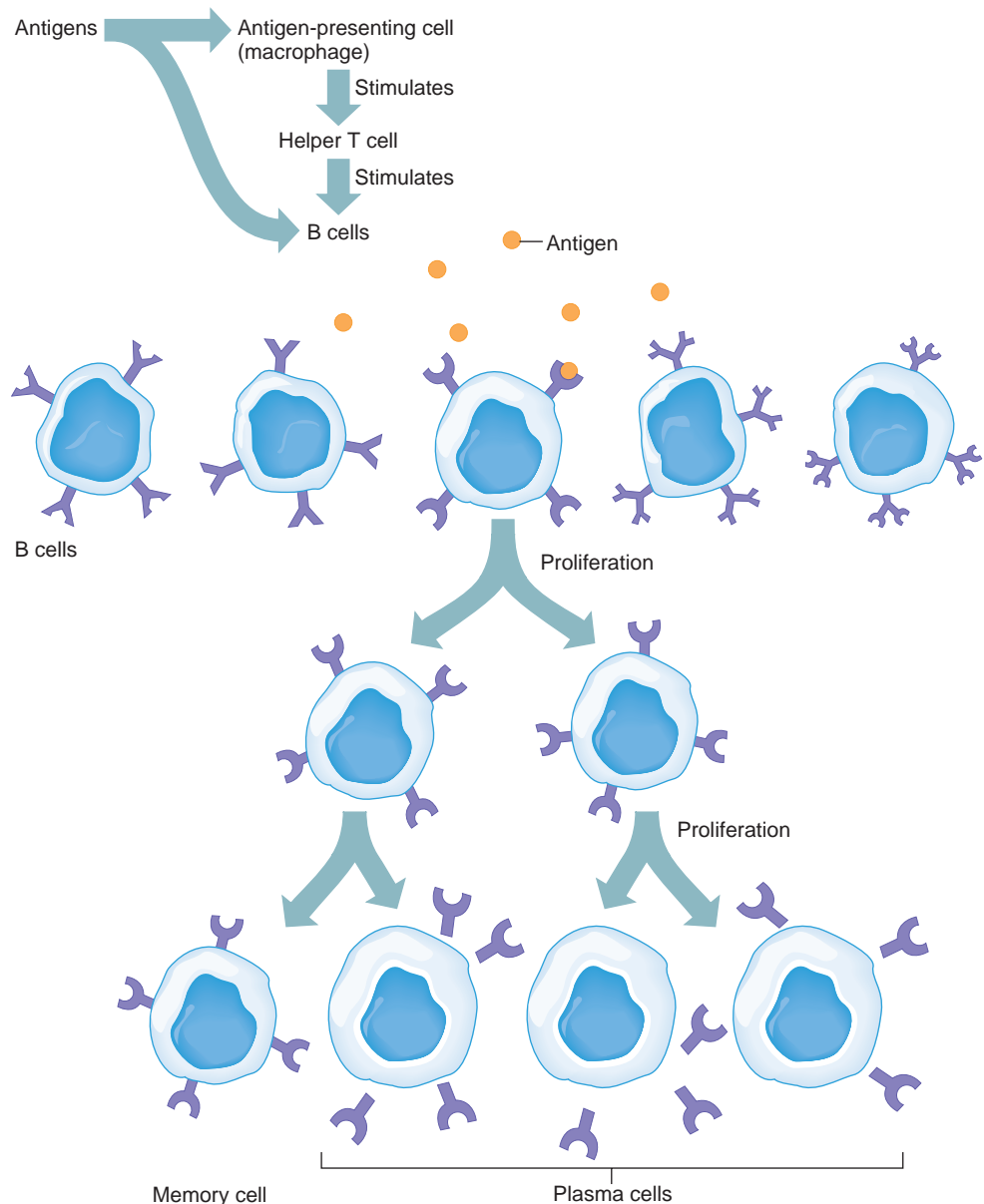
immune systems each season. RhoGAM given after an Rh incompatibility is discovered, but before the first baby is born, works because it blocks the primary immune response.

### The Humoral Immune Response—B Cells and Antibodies

An antibody response begins when an antigen-presenting macrophage activates a T cell. This cell in turn contacts a B cell that has surface receptors that can bind the type of foreign antigen the macrophage presents.

The immune system has so many B cells, each with different combinations of surface antigens, that there is almost always one or more available that corresponds to a particular foreign antigen. Turnover of these cells is high. Each day, millions of B cells perish in the lymph nodes and spleen, while millions more form in the bone marrow, each with a unique combination of surface molecules.

Once the activated T cell finds a B cell match, it releases cytokines that stimulate the B cell to divide. Soon the B cell gives rise to two types of cells (**figure 17.9**). The

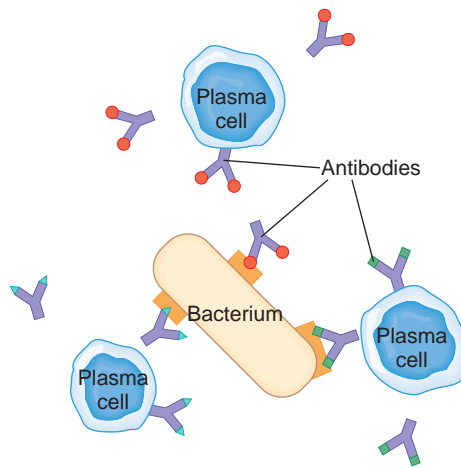


**Figure 17.9 Production of antibodies.** In the humoral immune response, B cells proliferate and mature into antibody-secreting plasma cells. Note that only the B cell that binds the antigen proliferates; its descendants may develop into memory cells or plasma cells. Plasma cells greatly outnumber memory cells.

first, plasma cells, are antibody factories, each secreting 1,000 to 2,000 identical antibodies per second into the bloodstream at the height of their few-day life span. These cells provide the primary immune response. Plasma cells derived from different B cells secrete different antibodies, with each type corresponding to a specific portion of the pathogen in what is called a polyclonal antibody response (**figure 17.10**). This response is like hitting a person in different parts of the body. The second type of B cell descendant, memory cells, are far fewer and usually dormant. They respond to the foreign antigen faster and with more force should it appear again. This is a secondary immune response.

An antibody molecule is constructed of several polypeptides and is therefore encoded by several genes. The simplest type of antibody molecule is four polypeptide chains connected by disulfide (sulfur-sulfur) bonds, forming a shape like the letter Y (**figure 17.11**). A large antibody molecule might consist of three, four, or five such Ys joined.

In a Y-shaped antibody subunit, the two longer polypeptides are called **heavy chains**, and the other two **light chains**. The lower portion of each chain is an amino



**Figure 17.10 An immune response recognizes many targets.** A humoral immune response is polyclonal, which means that different plasma cells produce antibody proteins that recognize and bind to different features of a foreign cell's surface.

acid sequence that is very similar in all antibody molecules, even in different species. These areas are called constant regions, and they provide the activity of the antibody. The amino acid sequences of the upper portions of each polypeptide chain, the variable regions, can differ greatly among

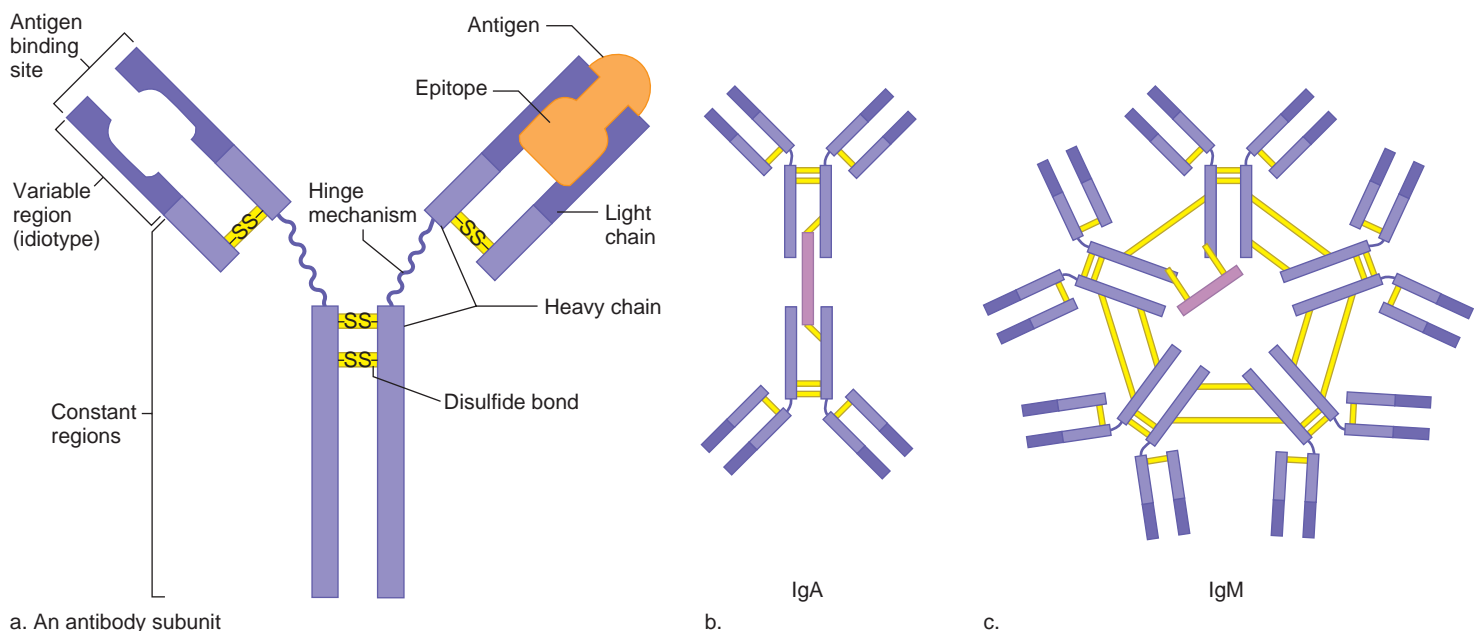
antibodies. These parts provide the specificities of particular antibodies to particular antigens.

Antibodies can bind certain antigens because of the three-dimensional shapes of the tips of the variable regions. These specialized ends are **antigen binding sites**, and the parts that actually contact the antigen are called **idiotypes**. The parts of the antigens that idiotype bind are **epitopes**. An antibody contorts to form a pocket around the antigen.

Antibodies have several functions. Antibody-antigen binding may inactivate a pathogen or neutralize the toxin it produces. Antibodies can clump pathogens, making them more visible to macrophages, which then destroy them. Antibodies also activate complement, extending the innate immune response.

Antibodies are of five major types, distinguished by location and function (**table 17.2**). (Antibodies are also called immunoglobulins, abbreviated *Ig*.) Different antibody types predominate in different stages of an infection.

The human body can manufacture seemingly limitless varieties of antibodies, though the genome has a limited number of antibody genes. This great diversity is



**Figure 17.11 Antibody structure.** The simplest antibody molecule (**a**) consists of four polypeptide chains, two heavy and two light, joined by two sulfur atoms that form a disulfide bond. Part of each polypeptide chain has a constant sequence of amino acids, and the remainder varies. The tops of the Y-shaped molecules form antigen binding sites. (**b**) IgA consists of two Y-shaped subunits, and IgM (**c**) consists of five subunits.

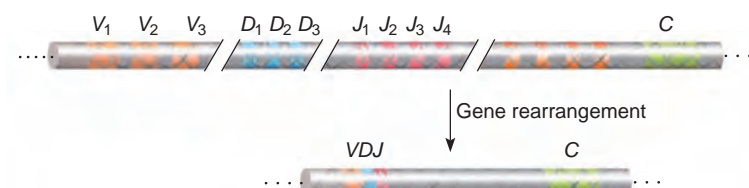
Table 17.2

## Types of Antibodies

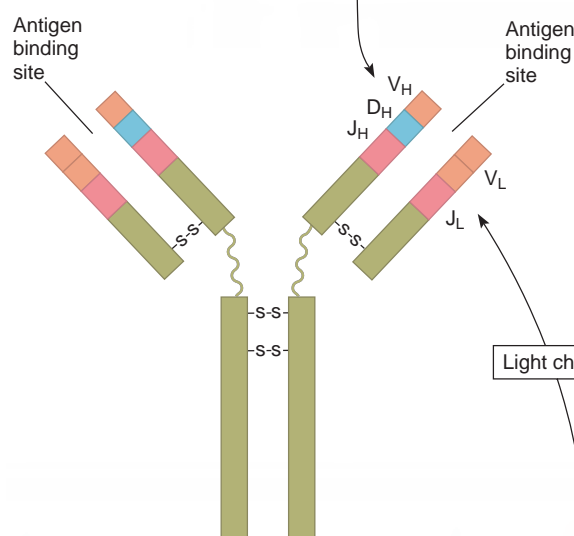
Type*	Location	Functions
IgA	Milk, saliva, urine, and tears; respiratory and digestive secretions	Protects against pathogens at points of entry into body
IgD	On B cells in blood	Stimulates B cells to make other types of antibodies, particularly in infants
IgE	In secretions with IgA and in mast cells in tissues	Acts as receptor for antigens that cause mast cells to secrete allergy mediators
IgG	Blood plasma and tissue fluid; passes to fetus	Protects against bacteria, viruses, and toxins, especially in secondary immune response
IgM	Blood plasma	Fights bacteria in primary immune response; includes anti-A and anti-B antibodies of ABO blood groups

\*The letters A, D, E, G, and M refer to the specific conformation of heavy chains characteristic of each class of antibody.

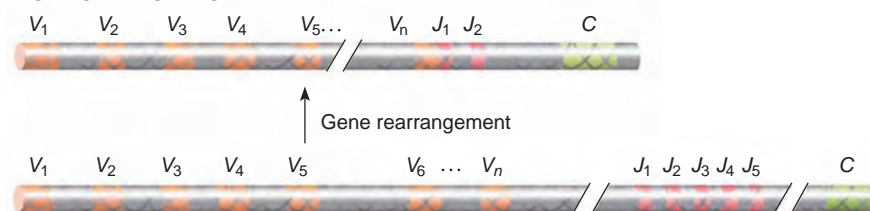
## HEAVY CHAIN GENES



## ANTIBODY STRUCTURE



## LIGHT CHAIN GENES



**Figure 17.12 Antibody diversity.** The human immune system can produce antibodies to millions of possible antigens because each polypeptide is encoded by more than one gene. That is, the many components of antibodies can combine in many ways.

possible because parts of different antibody genes combine. During the early development of B cells, sections of their antibody genes move to other chromosomal locations, creating new genetic instructions for antibodies.

The assembly of antibody molecules is like putting together many different outfits from the contents of a closet containing 200 pairs of pants, a drawer containing fifteen different shirts, and four belts. Specifically, each variable region of a heavy chain and a light chain consists of three sections, called V (for variable), D (for diversity), and J (for joining). The V, D, and J genes—several of each—for the heavy chains are on chromosome 14, and the corresponding genes for the light chains are on chromosomes 2 and 22. C (constant) genes encode the constant regions of each heavy and light chain. A promoter sequence precedes the V genes and an enhancer sequence precedes the C genes, and these control sequences oversee the mixing and matching of the V, D, and J genes. **Figure 17.12** shows how the genetic instructions for the antibody parts are combined in different ways to encode the heavy and light polypeptide chains.

Enzymes carry out the cutting and pasting that recombines antibody gene parts. This process apparently occurs at random, but the number of combinations is so great that virtually any antigen that a person with a healthy immune system might encounter will elicit an immune response.

### The Cellular Immune Response—T Cells and Cytokines

T cells provide the cellular immune response. It is called “cellular” because the T cells themselves travel to where they act, unlike B cells, which secrete antibodies into the bloodstream. T cells descend from stem cells in the bone marrow, then travel to the thymus gland (“T” refers to thymus). As the immature T cells, called thymocytes, migrate toward the interior of the thymus, they display diverse cell surface receptors. Then selection happens. As the wandering thymocytes touch lining cells in the gland that are studded with “self” antigens, thymocytes that do not attack the lining cells begin maturing into T cells, whereas those that harm the lining



cells die by apoptosis—in great numbers. Gradually, T-cells-to-be that recognize self persist while those that harm body cells are destroyed.

Several types of T cells are distinguished by the types and patterns of receptors on their surfaces, and by their functions. Helper T cells have many functions: they recognize foreign antigens on macrophages, stimulate B cells to produce antibodies, secrete cytokines, and activate another type of T cell called a cytotoxic T cell, (also called a killer T cell). Certain T cells may help to suppress an immune response when it is no longer required. The cytokines that helper T cells secrete include interleukins, interferons, tumor necrosis factor, and colony stimulating factors, which stimulate white blood cells in bone marrow to mature (**table 17.3**). Cytokines interact with and signal each other, sometimes in complex cascades.

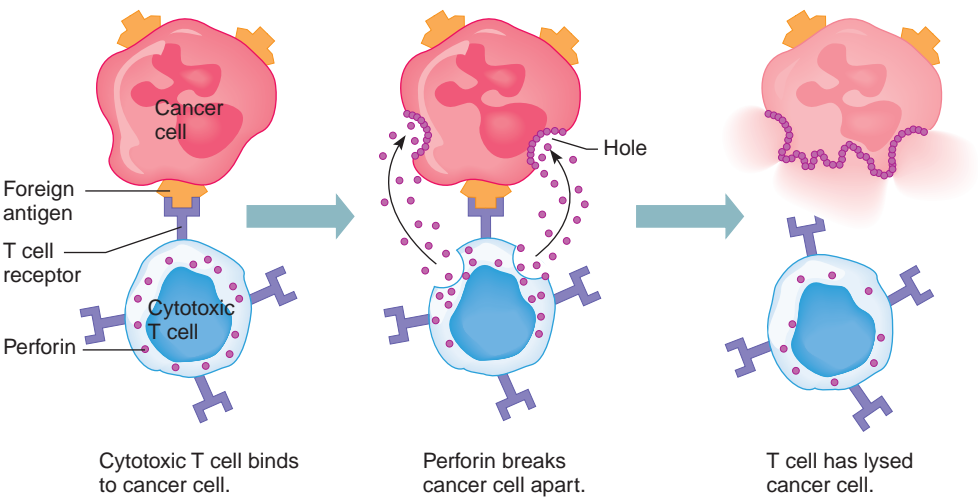
Distinctive surfaces distinguish subsets of helper T cells. Certain antigens called cluster-of-differentiation antigens, or CD antigens, enable T cells to recognize foreign antigens displayed on macrophages. One such cell type, called a CD4 helper T cell, is an early target of HIV. Considering the critical role helper T cells play in coordinating immunity, it is little wonder that HIV infection ultimately topples the entire system, a point we will return to soon.

Cytotoxic T cells lack CD4 receptors but have CD8 receptors. These cells attack virally infected and cancerous cells by attaching to them and releasing chemicals. They do this by linking two surface peptides to form structures called T cell receptors that bind foreign antigens. When a cytotoxic T cell encounters a non-self cell—a cancer cell, for example—the T cell receptors draw the two cells into physical contact. The T cell then releases a protein called perforin, which pierces the cancer cell's plasma membrane, killing it (**figure 17.13**). Cytotoxic T cell receptors also attract body cells that are covered with certain viruses, destroying the cells before the viruses on them can enter, replicate, and spread the infection. Cytotoxic T cells continually monitor body cells, recognizing and eliminating virally infected and tumor cells.

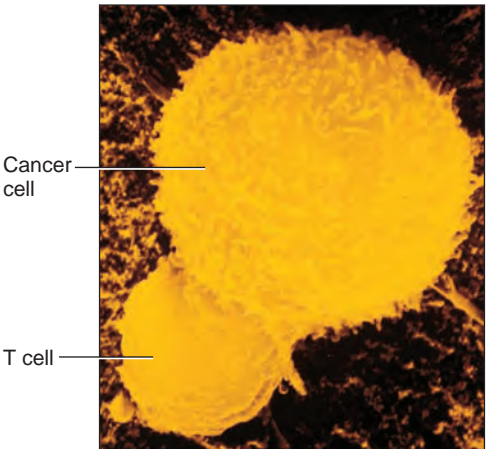
**Table 17.4** summarizes types of immune system cells.

**Table 17.3**  
**Types of Cytokines**

Cytokine	Function
Colony stimulating factors	Stimulate bone marrow to produce lymphocytes
Interferons	Block viral replication, stimulate macrophages to engulf viruses, stimulate B cells to produce antibodies, attack cancer cells
Interleukins	Control lymphocyte differentiation and growth, cause fever that accompanies bacterial infection
Tumor necrosis factor	Stops tumor growth, releases growth factors, stimulates lymphocyte differentiation, dismantles bacterial toxins



a.



b.

**Figure 17.13** **Death of a cancer cell.** (a) A cytotoxic T cell binds to a cancer cell and injects perforin, a protein that pierces (lyses) the cancer cell's plasma membrane. The cancer cell dies, leaving debris that macrophages clear away. (b) The smaller cell is a cytotoxic T cell, which homes in on the surface of the large cancer cell above it. The cytotoxic T cell will shatter the cancer cell, leaving scattered fibers.

Table 17.4

## Types of Immune System Cells

Cell Type	Function
Macrophage	Presents antigens Performs phagocytosis
Mast cell	Releases histamine in inflammation Releases allergy mediators
B cell	Matures into antibody-producing plasma cell or into memory cell
T cells	
Helper	Recognizes nonself antigens presented on macrophages Stimulates B cells to produce antibodies Secretes cytokines Activates cytotoxic T cells
Cytotoxic	Attacks cancer cells and cells infected with viruses upon recognizing antigens
Natural killer	Attacks cancer cells and cells infected with viruses without recognizing antigens; activates other white blood cells
Suppressor	Inhibits antibody production

## Key Concepts

1. The immune system consists of physical barriers; an innate immune response of inflammation, phagocytosis, complement, collectins, and cytokines; and an adaptive immune response that is diverse, specific, and remembers.
2. In the humoral immune response, stimulated B cells divide and differentiate into plasma cells and memory cells. A plasma cell secretes abundant antibodies of a single type. Antibodies are made of Y-shaped polypeptides, each consisting of two light and two heavy chains. Each chain consists of a constant and a variable region, and the tips of the Y form an antigen binding site with a specific idio type. Antibodies make foreign antigens more visible to macrophages and stimulate complement. Shuffling gene pieces generates great antibody diversity.
3. In the cellular immune response, helper T cells stimulate B cells to manufacture antibodies and cytotoxic T cells to secrete cytokines. Using T cell receptors, cytotoxic T cells bind to nonself cells and virus-covered cells and burst them.

## 17.3 Abnormal Immunity

The immune system continually adapts to environmental change. Because the immune response is so diverse, its breakdown affects health in many ways. Immune system malfunction may be inherited or acquired, and immunity may be too weak, too strong, or misdirected. Abnormal immune responses may be multifactorial, with several genes contributing to susceptibility to infection, or caused by mutation in a single gene. Or, susceptibility to an immune disorder may reflect abnormal gene expression, as the chapter opener describes for rheumatoid arthritis.

## Inherited Immune Deficiencies

The more than 20 types of inherited immune deficiencies affect innate and adaptive immunity (Table 17.5). These conditions can arise in several ways.

In chronic granulomatous disease, neutrophils can engulf bacteria, but, due to deficiency of an enzyme called an oxidase, they cannot produce the activated oxygen compounds that kill bacteria. Because this enzyme is made of four polypeptide chains, four genes encode it, and there are four

ways to inherit the disease, all X-linked. A very rare autosomal recessive form is caused by a defect in the part of the host cell that encloses bacteria. Antibiotics and gamma interferon are used to prevent bacterial infections in these patients, and the disease can be cured with a bone marrow or an umbilical cord stem cell transplant.

Mutations in genes that encode cytokines or T cell receptors impair cellular immunity, which primarily targets viruses and cancer cells. Because T cells activate the B cells that manufacture antibodies, abnormal cellular immunity (T cell function) disrupts humoral immunity (B cell function). Mutations in the genes that encode antibody segments, that control how the segments join, or that direct maturation of B cells mostly impair immunity against bacterial infection. Inherited immune deficiency can also result from defective B cells, which usually increases vulnerability to certain bacterial infections.

Severe combined immune deficiencies (SCID) affect both humoral and cellular immunity. About half of SCID cases are X-linked. In a less severe form, the individual lacks B cells but has some T cells. Before antibiotic drugs became available, individuals with this form of SCID died before age 10 of overwhelming bacterial infection. In a more severe form of X-linked SCID, lack of B and T cells causes death by 18 months of age, usually of severe and diverse infections. Gene therapy for X-linked SCID is effective, but in a few cases has caused leukemia by disrupting a cancer gene. An autosomal recessive form of SCID, adenosine deaminase deficiency, was the first illness successfully treated with gene therapy. Both disorders are discussed further in chapter 20.

A young man named David Vetter taught the world about the difficulty of life without immunity years before AIDS made it commonplace. David had an autosomal recessive form of SCID that caused him to be born without a thymus gland. His T cells could not mature and activate B cells, leaving him defenseless in a germ-filled world. Born in Texas in 1971, David spent his short life in a vinyl bubble, awaiting a treatment that never came (**figure 17.14**). As he reached adolescence, David wanted to leave his bubble. A bone marrow transplant was unsuccessful—soon afterward, David began vomiting and developed diarrhea, both



**Figure 17.14** David Vedder, the “bubble boy,” was born without a thymus gland. Because his T cells could not mature, he was virtually defenseless against infection.

signs of infection. David left the bubble, but died within days of a massive infection.

Inherited immune deficiency may also be very specific. For example, most people infected with herpes simplex virus develop cold sores, but in a few people, the virus infects the brain and may cause mental retardation, seizures, or death. French researchers found that many people with herpes simplex brain infections have parents who are related to each other. The researchers hypothesized that an autosomal recessive mutation might increase susceptibility to the severe form of the infection. Then the researchers learned of a mouse model of genetic disease that does not produce a certain type of interferon, and is at increased risk of contracting several types of infections, including the herpes brain infection. The human version of the gene also encodes this interferon, and the patients with the severe herpes infection indeed have mutations in both copies of this gene. Use of interferon to prevent the infection in genetically susceptible individuals is being tested.

### Acquired Immune Deficiency Syndrome

AIDS is not inherited, but acquired by infection with HIV, a virus that gradually shuts down the immune system (see figure 17.2b). First, HIV enters macrophages, impairing this first line of defense. In these cells and later in helper T cells, the virus adheres with its surface protein, called gp120, to two coreceptors on the host cell surface, CD4 and

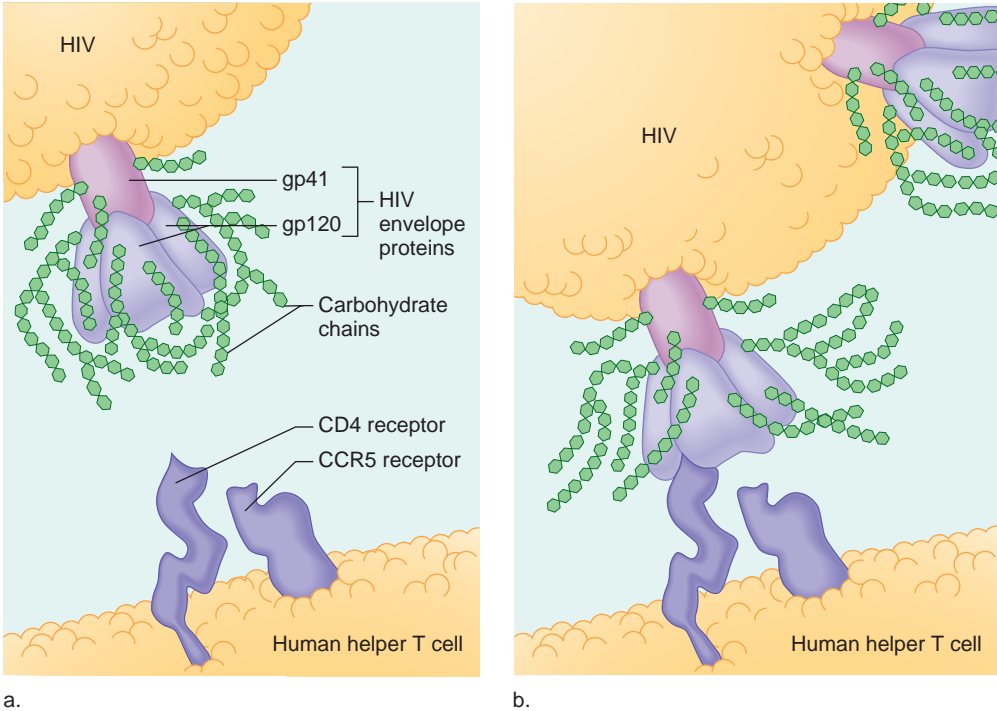
CCR5 (figure 17.15). Another glycoprotein, gp41, anchors gp120 molecules into the viral envelope. When the virus binds both coreceptors, virus and cell surface contour in

a way that enables viruses to enter the cell. Once in the cell, reverse transcriptase catalyzes construction of a DNA strand complementary to the viral RNA, which replicates

**Table 17.5**  
Inherited Immune Deficiencies

Disease	OMIM	Inheritance*	Defect
Chronic granulomatous disease	306400	ar, AD, xlr	Abnormal phagocytes can't kill engulfed bacteria
Immune defect due to absence of thymus	242700	ar	No thymus, no T cells
Neutrophil immunodeficiency syndrome	608203	ar	Deficiencies of T cells, B cells, and neutrophils
SCID			
Adenosine deaminase deficiency	102700	ar	No T or B cells
Adenosine deaminase deficiency with sensitivity to ionizing radiation	602450	ar	No T, B, or natural killer cells
IL-2 receptor mutation	300400	xlr	No T, B, or natural killer cells

\*ar = autosomal recessive  
AD = autosomal dominant  
xlr = X-linked recessive



**Figure 17.15** HIV binds to a helper T cell. (a) The part of HIV that binds to helper T cells is called gp120 (gp stands for glycoprotein). (b) The carbohydrate chains that shield the protein portion of gp120 move aside as they approach the cell surface, and the viral molecule can now bind to a CD4 receptor. Binding to the CCR5 receptor is also necessary. Then the viral envelope fuses with the plasma membrane and the virus enters. (The size of HIV is greatly exaggerated.)



to form a DNA double helix. This enters the nucleus and inserts into a chromosome. The viral DNA sequences are transcribed and translated, and the cell fills with viral pieces, which are assembled into complete new viral particles that eventually bud from the cell (figure 17.16).

Once helper T cells start to die at a high rate, bacterial infections begin, because B cells aren't activated to produce antibodies. Much later in infection, HIV variants arise that can bind to a receptor called CXCR4 on cytotoxic T cells, killing them. Loss of these cells renders the body very vulnerable to viral infections and cancer.

HIV replicates quickly, changes quickly, and can hide. The virus mutates easily because it cannot repair replication errors and errors happen frequently—1 per every 5,000 or so bases—because of the “sloppiness” of reverse transcriptase in copying viral RNA into DNA. The immune system cannot keep up; antibodies against one viral variant are useless against the next. For several years, the bone marrow produces 2 billion new T and B cells a day. A million to a billion new HIV particles bud daily from infected cells.

So genetically diverse is the population of HIV in a human host that, within days of the initial infection, variants arise that resist the drugs used to treat AIDS (see figure 15.11). HIV's changeable nature has important clinical implications. Combining drugs with different actions is the most effective way to slow the disease process, so that AIDS becomes a chronic, lifelong, but treatable illness, instead of a killer (table 17.6). Three types of drugs have cut the death rate from AIDS dramatically.

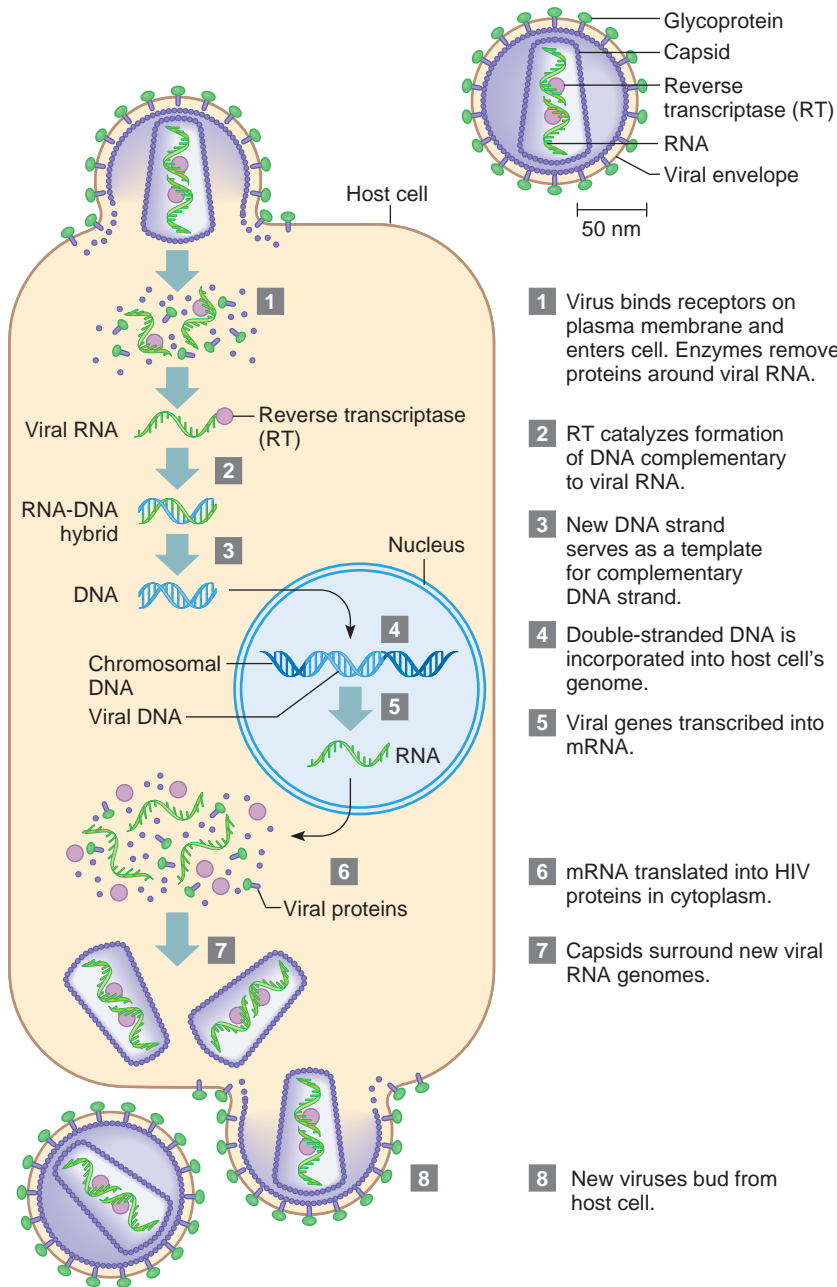
Clues to developing new drugs to treat HIV infection come from people at high risk who resist infection. For example, researchers have identified variants of four receptors or the molecules that bind to them that block HIV from entering cells. To identify these receptors, researchers scrutinized the DNA of people who had unprotected sex with many partners, and people with hemophilia who had received HIV-tainted blood in the 1980s—but who were not infected. Some of them were homozygous recessive for a 32-base deletion in the *CCR5* gene. Their CCR5 coreceptors were too stunted, thanks to a premature “stop” codon, to

reach the cell's surface. Like a ferry arriving at shore to find no dock, HIV has nowhere to bind on the cells of these fortunate

individuals. Heterozygotes, with one copy of the deletion, can become infected with HIV, but they remain healthy for several

**Table 17.6**  
**Anti-HIV Drugs**

Drug Type	Mechanism
Reverse transcriptase inhibitor	Blocks copying of viral RNA into DNA
Protease inhibitor	Blocks shortening of certain viral proteins
Entry inhibitor	Blocks ability of HIV to bind, fuse with, and enter a cell



**Figure 17.16** **How HIV infects.** HIV integrates into the host chromosome, then commandeers transcription and translation, ultimately producing more virus particles.

years longer than people who do not have the deletion. Curiously, the same *CCR5* mutation may have enabled people to survive plague in Europe during the Middle Ages. Apparently both the virus that causes AIDS and the bacterium that causes plague use the same portal into a human cell.

## Autoimmunity

Autoimmunity is a reaction that occurs when the immune system produces antibodies, called **autoantibodies**, that attack the body's own healthy tissues. About 5 percent of the population has an autoimmune disorder. Usually, these conditions “run in families” but are not Mendelian, indicating that several genes and environmental factors may be at play. However, a mutation in a single gene can increase the risk of developing several autoimmune disorders in a family. For example, mutations in a gene called *FCRL3* (OMIM 606510) are associated with rheumatoid arthritis, systemic lupus erythematosus, Graves disease, and Hashimoto's thyroiditis.

The signs and symptoms of autoimmune disorders reflect the cell types under attack. For example, autoimmune ulcerative colitis affects colon cells, causing severe abdominal pain.

A mutation in a single gene may cause varied autoimmune symptoms. For example, a mutation in a gene on chromosome 21q causes autoimmune polyendocrinopathy syndrome type I (OMIM 240300), in which endocrine glands malfunction in a sequence. Children under 5 develop candidiasis, a fungal infection (not an autoimmune disorder). By age 10, the individual's parathyroid glands begin to fail, affecting calcium metabolism. By age 15, most affected individuals also develop Addison disease, a deficiency in adrenal gland hormones. Other associated conditions include thyroid deficiency, diabetes mellitus, vitiligo (skin whitening), and alopecia (hair loss).

The symptoms of many autoimmune conditions can arise by any of several mechanisms, making diagnosis difficult. Hemolytic anemia, for example, may be autoimmune, inherited, or a reaction to toxin exposure.

Autoimmunity may arise in several ways:

- A virus replicating within a cell incorporates proteins from the cell's

surface onto its own. When the immune system “learns” the surface of the virus to destroy it, it also learns to attack human cells that normally bear the protein.

- Some thymocytes that should have died in the thymus somehow escape the massive die-off, persisting to attack “self” tissue later on.
- A nonself antigen coincidentally resembles a self antigen, and the immune system attacks both. In rheumatic fever, for example, antigens on heart valve cells resemble those on *Streptococcus* bacteria; antibodies produced to fight a strep throat also attack the heart valve cells.
- If X inactivation is skewed, a female may have a minority of cells that express the X chromosome genes of one parent. The immune system may respond to these cells as foreign if they have surface antigens that are not also on the majority of cells. Skewed X inactivation may explain why some autoimmune disorders are much more common in females.

Some disorders thought to be autoimmune may in fact have a more bizarre cause—fetal cells persisting in a woman's circulation, even decades after her offspring has grown up! In response to an as yet unknown trigger, the fetal cells, perhaps “hiding” in a tissue such as skin, emerge, stimulating antibody production and symptoms in the mother. This mechanism, called microchimerism (“small mosaic”), may explain the higher prevalence of autoimmune disorders among women. It was discovered in a disorder called scleroderma, which means “hard skin” (**figure 17.17**).

Patients describe scleroderma, which typically begins between ages 45 and 55, as “the body turning to stone.” Symptoms include fatigue, swollen joints, stiff fingers, and a masklike face. The hardening may also affect blood vessels, the lungs, and the esophagus. Clues that scleroderma is a delayed response to persisting fetal cells include the following observations:

- It is much more common in women.
- Symptoms resemble those of graft-versus-host disease (GVHD), in which



**Figure 17.17 An autoimmune disorder—maybe.** Scleroderma hardens the skin. Some cases appear to be caused by a long-delayed immune response to cells retained from a fetus decades earlier.

transplanted tissue produces chemicals that destroy the host's body. Antigens on cells in scleroderma lesions match those that cause GVHD.

- Mothers who have scleroderma have cell surfaces that are more similar to those of their sons than those of unaffected mothers and their sons. Perhaps the similarity of cell surfaces enabled the fetal cells to escape destruction by the woman's immune system.
- Skin lesions from affected mothers of sons include cells that have Y chromosomes. Mothers can develop scleroderma from daughters too, but the fetal cells cannot be as easily distinguished because they are XX, like the mothers' cells.

It's possible that other disorders traditionally considered autoimmune and that are more prevalent in women may actually reflect an immune system response to lingering fetal cells.

## Allergies

An allergy is an immune system response to a substance, called an allergen, that does not actually present a threat. Many allergens are particles small enough to be carried in the air and enter a person's respiratory tract.

The size of the allergen may determine the type of allergy. For example, grass pollen is large and remains in the upper respiratory tract, where it causes hay fever. But allergens from house dust mites, cat dander, and cockroaches are small enough to infiltrate the lungs, triggering asthma. Asthma is a chronic disease in which contractions of the airways, inflammation, and accumulation of mucus block air flow.

Both humoral and cellular immunity take part in an allergic response (**figure 17.18**). Antibodies of class IgE bind to mast cells, sending signals that cause the mast cells to open and release allergy mediators such as histamine and heparin. Allergy mediators cause inflammation, with symptoms that may include runny eyes from hay fever, narrowed airways from asthma, rashes, or the overwhelming body-wide allergic reaction called anaphylactic shock. Allergens also activate a class of helper T cells that produce a particular mix of cytokines whose genes are clustered on chromosome 5q. Regions of chromosomes 12q and 17q have genes that control IgE production.

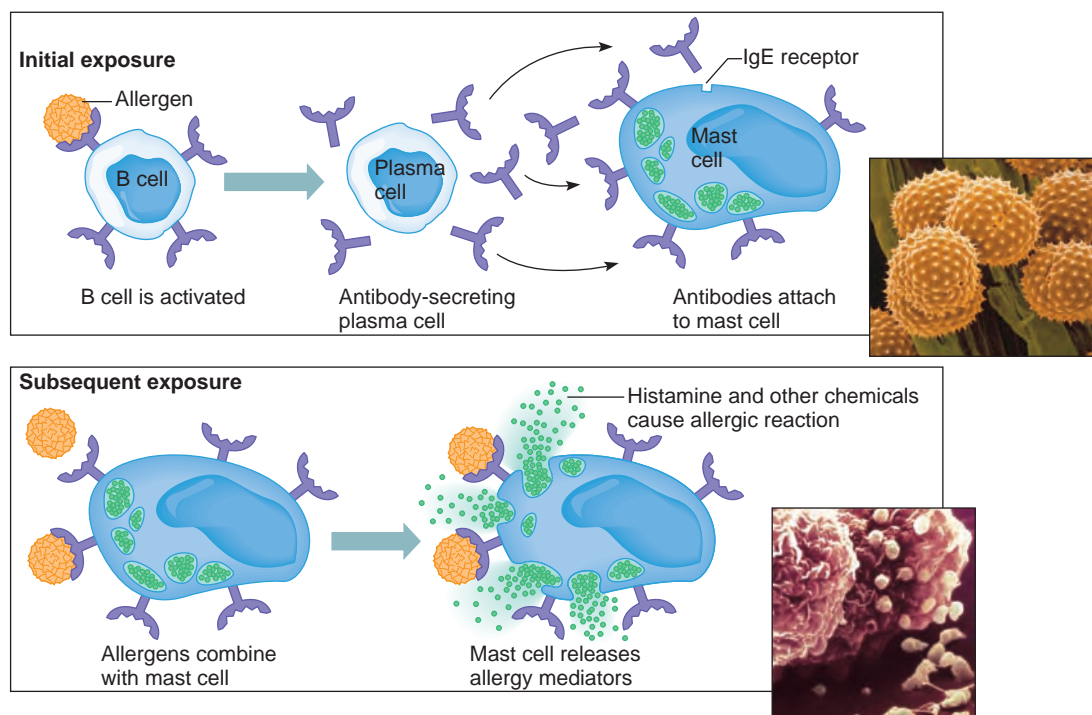
The fact that allergies have become very common only during the past century

suggests a much stronger environmental than genetic component. Still, people inherit susceptibilities to allergy. Twin studies of various allergies reveal about a 75 percent concordance, and isolated populations with a great deal of inbreeding tend to have a high prevalence of certain allergies.

The allergies that people suffer today may be a holdover of an immune function that was important in the past. Evidence for this idea is that people with allergies have higher levels of white blood cells called eosinophils than do others, and these cells fight parasitic infections that are no longer common. In a more general sense, because allergies are more prevalent in developed nations and have become more prevalent since the introduction of antibiotic drugs, some researchers hypothesize that allergies may result from a childhood relatively free of infection, compared to times past—almost as if the immune system is reacting to being underutilized. This idea that allergies stem from an environment too clean to have stimulated the immune system very much is called the hygiene hypothesis.

## Key Concepts

1. Inherited immune deficiencies affect innate and adaptive immunity.
2. HIV is a retrovirus that injects its RNA into host cells by binding coreceptors. Reverse transcriptase then copies viral RNA into DNA. HIV uses the cell's protein synthesis machinery to mass produce itself; then the cell releases virus. HIV continually mutates, becoming resistant to drugs. HIV replicates very rapidly, and T cell production matches it until the immune response is overwhelmed.
3. In autoimmune disorders, autoantibodies attack healthy tissue. These conditions may be caused by a virus that borrows a self antigen, T cells that never recognize self, or healthy cells bearing antigens that resemble nonself antigens. Some conditions considered autoimmune may be a response to retained fetal cells.
4. An overly sensitive immune system causes allergies.
5. Allergens bind to IgE antibodies on mast cells, which release allergy mediators. A subset of helper T cells secretes cytokines that contribute to allergy symptoms.



**Figure 17.18 Allergy.** In an allergic reaction, an allergen such as pollen (upper inset) activates B cells, which divide and give rise to antibody-secreting plasma cells. The antibodies attach to mast cells. When the person encounters allergens again, the allergens combine with the antibodies on the mast cells, which then burst (lower inset), releasing the chemicals that cause itchy eyes and a runny nose.



## 17.4 Altering Immune Function

Medical technology can alter or augment immune system functions in various ways. Vaccines trick the immune system into acting early. Antibiotic drugs, which are substances derived from organisms such as fungi and soil bacteria, have been used for decades to assist an immune response. Cytokines and altered antibodies are used as drugs to treat a variety of conditions. Transplants require suppression of the immune system so that the body will accept a nonself replacement body part.

### Vaccines

A **vaccine** is an inactive or partial form of a pathogen that stimulates the immune system to alert B cells to produce antibodies. When the person then encounters the natural pathogen, a secondary immune response ensues, even before symptoms arise. Vaccines consisting of entire viruses or bacteria can, rarely, cause illness if they mutate to a pathogenic form. This was a risk of the smallpox vaccine. A safer vaccine uses only the part of the pathogen's surface that elicits an immune response. Vaccines against different illnesses can be combined into one injection, or the genes encoding antigens from several pathogens can be inserted into a harmless virus and delivered as a "super vaccine."

Vaccine technology dates back to the eleventh century in China. Because people saw that those who recovered from smallpox never got it again, they crushed scabs into a powder that they inhaled or rubbed into pricked skin. In 1796, the wife of a British ambassador to Turkey witnessed the Chinese method of vaccination and mentioned it to English country physician Edward Jenner. Intrigued, Jenner was vaccinated the Chinese way, and then thought of a different approach.

It was widely known that people who milked cows contracted a mild illness called cowpox, but did not get smallpox. The cows became ill from infected horses. Since the virus seemed to jump from one species to another, Jenner wondered whether exposing a healthy person to cowpox lesions might protect against smallpox. A slightly different virus causes cowpox, but Jenner's

approach worked, leading to development of the first vaccine (the word comes from the Latin *vacca*, for "cow"). Jenner tried his first vaccine on a volunteer, 8-year-old James Phipps. Jenner dipped a needle in pus oozing from a small cowpox sore on a milkmaid named Sarah Nelmes, then scratched the boy's arm with it. He then exposed the boy to people with smallpox. Young James never became ill. Eventually, improved versions of Jenner's smallpox vaccine eradicated a disease that once killed millions. (**figure 17.19**). By the 1970s, vaccination became unnecessary. However, several nations have resumed smallpox vaccination, as section 17.5 discusses.

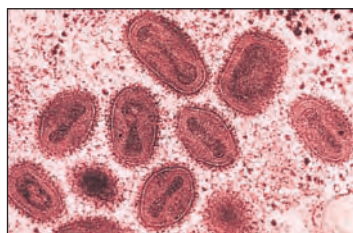
People still receive most vaccines as injections, such as the vaccine given to girls to protect against four strains of human papillomavirus that can cause cervical cancer. New delivery methods include nasal sprays (flu vaccine) and genetically modified fruits and vegetables. A banana as a vaccine makes sense in theory, but in practice it is proving difficult to obtain a uniform product. Edible plants are grown from cells that

are given genes from pathogens that encode the antigens that evoke an immune response. When the plant vaccine is eaten, the foreign antigens stimulate phagocytes beneath the small intestinal lining to "present" the antigens to nearby T cells. From here, the antigens are passed to the bloodstream, where they stimulate B cells to divide to yield plasma cells that produce IgA. These antibodies coat the small intestinal lining, protecting against pathogens in food. Current research focuses on converting plant-based vaccines into powders so that doses can be regulated—but this counters the original goal of easily immunizing babies in developing countries with bananas.

Whatever the form of vaccine, it is important that a substantial proportion of a population be vaccinated. This establishes "herd immunity"—that is, if unvaccinated people are rare, then if the pathogen appears, it does not spread, because so many people are protected. If the population includes connected pockets of unvaccinated individuals, the disease can spread.



a.



b.

0.1  $\mu$ m



c.

**Figure 17.19 Smallpox: Gone?** (a) Edward Jenner invented the modern version of a smallpox (b) vaccine in 1798. (c) This boy is one of the last victims of smallpox, which has not naturally infected a human since 1977. Because many doctors are unfamiliar with smallpox, and people are no longer vaccinated, an outbreak would be a major health disaster.

## Immunotherapy

Immunotherapy amplifies or redirects the immune response. It originated in the nineteenth century to treat disease. Today, a few immunotherapies are in use, with more in clinical trials.

### Monoclonal Antibodies Boost Humoral Immunity

When a B cell recognizes a single foreign antigen, it manufactures a single, or monoclonal, type of antibody. A large amount of a single antibody type could target a particular pathogen or cancer cell because of the antibody's great specificity.

In 1975, British researchers Cesar Milstein and George Köhler devised **monoclonal antibody (MAb) technology**, which mass-produces a single B cell, preserving its specificity and amplifying its antibody type. First, they injected a mouse with a sheep's red blood cells (**figure 17.20**). They then isolated a single B cell from the mouse's spleen and fused it with a cancerous white blood cell from a mouse. The fused cell, called a hybridoma, had a valuable pair of talents. Like the B cell, it produced large amounts of a single antibody type. Like the cancer cell, it divided continuously.

Today MAbs are made to more closely resemble natural human antibodies because the original mouse preparations caused allergic reactions. MAbs are used in basic research, veterinary and human health care, agriculture, forestry, and forensics. MAbs are used to diagnose everything from strep throat to turf grass disease. In a home pregnancy test, a woman places drops of her urine onto a paper strip containing a MAb that binds hCG, the "pregnancy" hormone. The color changes if the MAb binds its target. In cancer diagnosis, if a MAb attached to a fluorescent dye and injected into a patient or applied to a sample of tissue or body fluid binds its target—an antigen found mostly or only on cancer cells—fluorescence indicates disease. MAbs linked to radioactive isotopes

**Figure 17.20 Monoclonal antibody technology.** Monoclonal antibodies are pure preparations of a single antibody type that recognize a single antigen type. They are useful in diagnosing and treating disease because of their specificity.

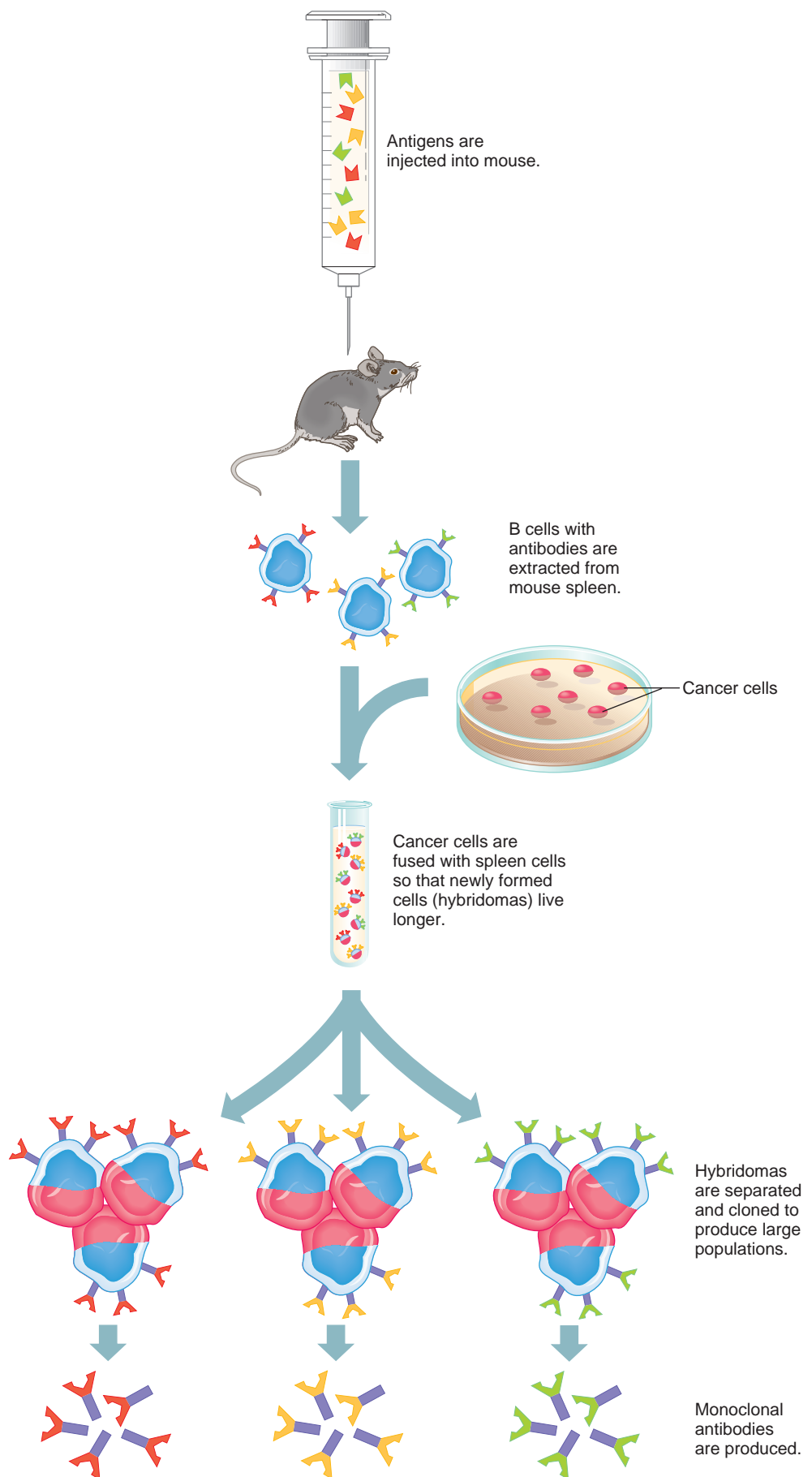


Table 17.7

## Drugs Based on Monoclonal Antibodies

Drug	Disease	Mechanism
Tysabri	Multiple sclerosis	Binds cells that produce autoantibodies against brain and/or spinal cord tissue
Erbix	Colorectal cancer	Blocks growth factor receptor overabundant on cancer cells, preventing cell division
Avastin	Colorectal cancer	Blocks growth factor from attracting nearby blood vessels to tumor
Raptiva	Psoriasis	Blocks T cell functions
Xolair	Asthma	Blocks IgE, preventing allergic response
Synagis	Respiratory syncytial virus infection	Binds virus
Remicade	Crohn disease	Blocks excess tumor necrosis factor
	Rheumatoid arthritis	

or to drugs deliver treatment to cancer cells. For example, a MAb-based drug called Herceptin blocks receptors on certain breast cancer cell surfaces, preventing them from receiving signals to divide. **Table 17.7** describes a few MAb-based drugs.

### Cytokines Boost Cellular Immunity

As coordinators of immunity, cytokines are used to treat a variety of conditions. However, it has been difficult to develop these body chemicals into drugs because they remain active only for short periods. They must be delivered precisely where they are needed, or overdose or side effects can occur.

Interferon (IF) was the first cytokine tested on a large scale. Various interferons are used to treat cancer, genital warts, and multiple sclerosis. Interleukin-2 (IL-2) is administered intravenously to treat kidney cancer recurrence. Colony stimulating factors, which cause immature white blood cells to mature and differentiate, boost white blood cell levels in people with suppressed immune systems, such as individuals with AIDS or receiving cancer chemotherapy. This enables a patient to withstand higher doses of a conventional drug.

Because excess tumor necrosis factor (TNF) underlies some disorders, blocking its activity treats some conditions. The drug Enbrel, for example, consists of part of a receptor for TNF. Taking it prevents TNF from binding to cells that line joints,

relieving arthritis. Excess TNF in rheumatoid arthritis prevents the joint lining cells from secreting lubricating fluid.

### Transplants

When a car breaks down, replacing the damaged part often fixes the trouble. The same is sometimes true for the human body. Hearts, kidneys, livers, lungs, corneas, pancreases, skin, and bone marrow are routinely transplanted, sometimes several organs at a time. Although transplant medicine had a shaky start (see the **Technology Timeline: Transplantation** on page 346.), many problems have been solved. Today, thousands of transplants are performed annually and recipients gain years of life. The challenge to successful transplantation lies in genetics because individual inherited differences in cell surfaces determine whether the body will accept tissue from a particular donor.

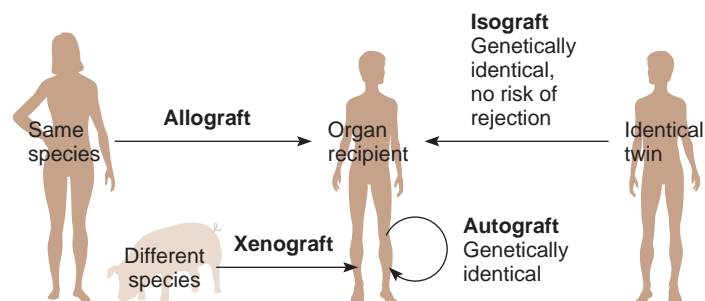
### Transplant Types

Transplants are classified by the relationship of donor to recipient (**figure 17.21**):

1. An autograft transfers tissue from one part of a person's body to another. A skin graft taken from the thigh to replace burned skin on the chest, or a leg vein that replaces a coronary artery, are autografts. The immune system does not reject the graft because the tissue is self. (Technically, an autograft is not a transplant because it involves only one person.)
2. An isograft is tissue from a monozygotic twin. Because the twins are genetically identical, the recipient's immune system does not reject the transplant. Ovary isografts have been performed.
3. An allograft comes from an individual who is not genetically identical to the recipient, but is a member of the same species. A kidney transplant from an unrelated donor is an allograft.
4. A xenograft transplants tissue from one species to another. (See the Bioethics Box on page 347.)

### Rejection Reactions—Or Acceptance

The immune system recognizes most donor tissue as nonself. Then, in a tissue rejection reaction, T cells, antibodies, and activated complement destroy the foreign tissue. The greater the difference between recipient and donor cell surfaces, the more rapid and severe the rejection reaction. An extreme example is the hyperacute rejection



**Figure 17.21 Transplant types.** An autograft is within an individual. An isograft is between identical twins. An allograft is between members of the same species, and a xenograft is between members of different species.



# Technology Timeline

## Transplantation

<b>1899</b>	First allograft—a kidney from dog to dog.
<b>1902</b>	Pig kidney is attached to blood vessels of a woman dying of kidney failure.
<b>1905</b>	First successful corneal transplant, from a boy who lost an eye in an accident to a man whose cornea was chemically damaged. Works because cornea cells lack antigens.
<b>1906</b>	First attempted kidney transplant fails.
<b>1940s</b>	First kidney transplants on young people with end-stage kidney failure.
<b>1950s</b>	Blood typing predicts success of donor-recipient pairs for organ transplants. Invention of heart-lung bypass machine makes heart transplants feasible.
<b>1954</b>	First successful organ transplant, of a kidney from a MZ twin.
<b>1960s</b>	First effective immunosuppressant drugs developed. Heart transplants performed in dogs with mixed success.
<b>1967</b>	First human heart transplant. Patient lives 18 days.
<b>1968</b>	Uniform Anatomical Gift Act passes. Requires informed consent from next of kin before organs or tissues can be donated.
<b>1970s</b>	Transplant problems: they extend life only briefly and do not correct underlying disease; surgical complications; rejection reactions. Many hospitals ban transplants.
<b>1980s</b>	Improved immunosuppressant drugs, surgical techniques, and tissue matching, plus the ability to strip antigens from donor tissue, reawaken interest in transplants.
<b>1984</b>	Doctors transplant a baboon's heart into "Baby Fae," who was born with half a heart. She lives 20 days before rejecting the xenograft.
<b>1992</b>	Surgeons transplant a baboon liver into a 35-year-old man with hepatitis. The man lives for 71 days, dying of an unrelated cause. Researchers realize lower doses of anti-rejection drugs may improve survival.
<b>1997</b>	Pig cell implants used to treat pancreatic failure and Parkinson disease. Pig liver used to maintain liver function for six hours as young man awaited a human liver.
<b>1998</b>	Transplants of hands and forearms begin.
<b>2000</b>	Cloning of pigs brings xenotransplantation closer to reality.
<b>2003</b>	Cloned mini-pigs genetically modified to lack cell surface molecules that provoke human immune response.
<b>2003</b>	DNA gene expression microarrays predict which patients are likely to reject kidney transplants.
<b>2004</b>	Researchers discover that infants have a better chance of accepting a heart transplant because their immune systems are not as mature.
<b>2006</b>	First face transplant.
<b>Future</b>	Tissue engineering, perhaps using stem cells from patients, others, or embryos, may replace transplantation.

reaction against tissue transplanted from another species—the donor tissue is usually destroyed in minutes as blood vessels blacken and cut off the blood supply.

Physicians use several approaches to dampen rejection so that a transplant

recipient can survive. These include closely matching the HLA types of donor and recipient and stripping donor tissue of antigens. Newer immunosuppressive drugs inhibit production of the antibodies and T cells that specifically attack transplanted tissue, while

sparing other components of the immune system. Experiments on transplanted tissues using gene expression microarrays reveal at least three types of rejection not otherwise obvious. Such profiling will likely be used to better match donors to recipients.

Rejection is not the only problem that can arise from an organ transplant. Graft-versus-host disease develops sometimes when bone marrow transplants are used to correct certain blood deficiencies and cancers. The transplanted bone marrow, which is actually part of the donor's immune system, attacks the recipient—its new body—as foreign. Symptoms include rash, abdominal pain, nausea, vomiting, hair loss, and jaundice.

Sometimes a problem arises if a bone marrow transplant to treat cancer is too closely matched to the recipient. This may at first seem illogical, but what happens is that if the cancer returns with the same cell surfaces as it had earlier, the patient's new bone marrow is so similar to the old marrow that it is equally unable to fight the cancer. The best tissue for transplant may be highly similar, but not identical, to the recipient's tissues. That is, the donor bone marrow should be different enough to control the cancer, but not so different that rejection occurs.

## Key Concepts

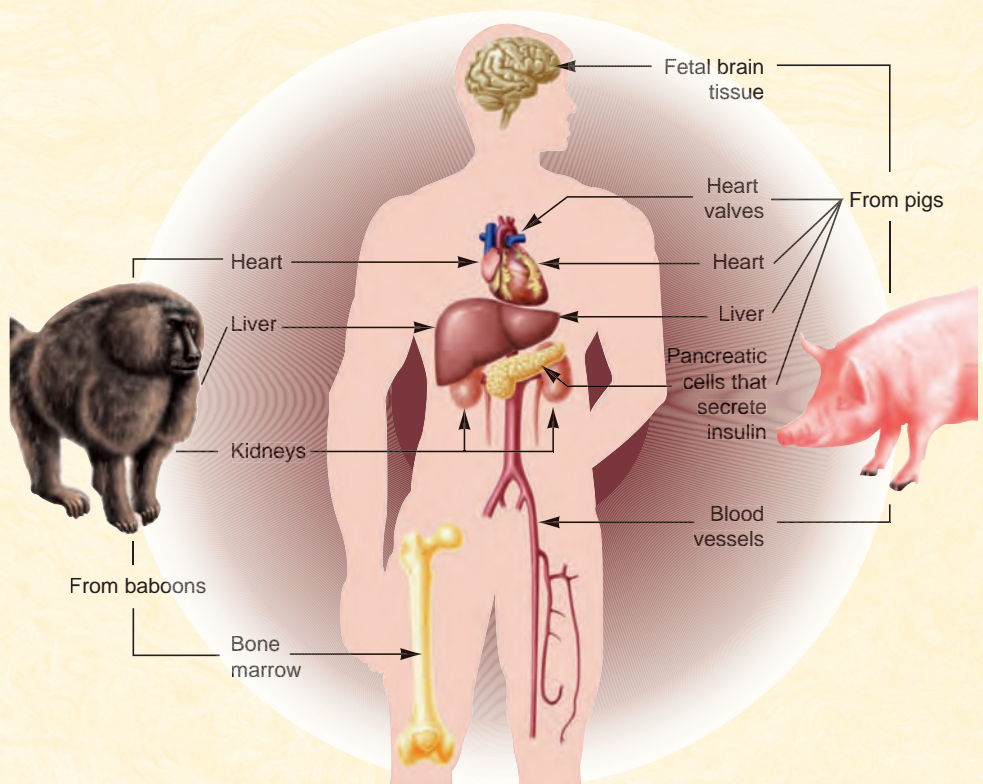
1. Vaccines are disabled pathogens or their parts that elicit an immune response, protecting against infection by the active pathogen.
2. Immunotherapy uses immune system components to fight disease. B cells fused with cancer cells produce MAbs that target specific antigens. Cytokines boost immune function and destroy cancer cells.
3. Autografts transfer tissue from one part of a person's body to another; isografts are between identical twins; allografts are between members of the same species; and a xenograft is a cross-species transplant.
4. Allografts can cause tissue rejection reactions, and xenografts can set off hyperacute rejection. In graft-versus-host disease, transplanted bone marrow rejects the recipient's tissues.

## Pig Parts

In 1902, a German medical journal reported an astonishing experiment. A physician, Emmerich Ullman, had attached the blood vessels of a patient dying of kidney failure to a pig's kidney set up by her bedside. The experiment failed when the patient's immune system rejected the attachment almost immediately.

Nearly a century later, in 1997, an eerily similar experiment took place. Robert Pennington, a 19-year-old suffering from acute liver failure and desperately needing a transplant, survived for six and a half hours with his blood circulating outside of his body through a living liver removed from a 15-week-old, 118-pound pig named Sweetie Pie. The pig liver served as a bridge until a human liver became available. But Sweetie Pie was no ordinary pig. She had been genetically modified and bred so that her cells displayed a human protein that controlled rejection of tissue transplanted from an animal of another species. Because of this slight but key bit of added humanity, plus immunosuppressant drugs, Pennington's body tolerated the pig liver's help for the few crucial hours. Baboons have also been used as sources of transplant organs (**figure 1**).

Successful xenotransplants would help alleviate the organ shortage. However, some people object to raising animals to use their organs as transplants because it requires killing the donors. One researcher counters such protests by comparing the use of animal organs to eating them.



**Figure 1** Baboons and pigs can provide tissues and organs for transplant.

A possible danger of xenotransplants is that people may acquire viruses from the donor organs. Viruses can “jump” species, and the outcome in the new host is unpredictable. For example, a virus called PERV—for “porcine endogenous retrovirus”—can infect human cells in culture. However, several dozen patients who received implants of pig tissue did not show

evidence of PERV years later. That study, though, looked only at blood. We still do not know what effect pig viruses can have on a human body. Because many viral infections take years to cause symptoms, introducing a new infectious disease in the future could be the trade-off for using xenotransplants to solve the current organ shortage.

## 17.5 A Genomic View of Immunity—The Pathogen's Perspective

Immunity against infectious disease involves interactions of two genomes—ours and the pathogen's. Human genome information is revealing how the immune system halts infectious disease. Information from pathogen genomes reveals how they

make us sick. **Table 17.8** lists some of the pathogens whose genomes have been sequenced.

Knowing the DNA sequence of a pathogen's genome, or the sequences of key genes, can reveal exactly how that organism causes illness in humans, which can suggest new treatment strategies. The sequence for *Streptococcus pneumoniae*, for example, revealed instructions for a huge protein that

enables the bacterium to adhere to human cells. Potential drugs could dismantle this adhesion protein.

Pathogen genome information is also used to protect against infection in an approach called reverse vaccinology. Instead of culturing hard-to-grow pathogens in the laboratory, researchers scan genome sequences and identify parts that encode antigens that provoke the human immune



Table 17.8

## Pathogens with Sequenced Genomes

Pathogen	Human Disease
<b>Bacterial</b>	
<i>Borrelia burgdorferi</i>	Lyme disease
<i>Brucella suis</i>	Fever (infertility in other animals)
<i>Campylobacter jejuni</i>	Food poisoning
<i>Clostridium perfringens</i>	Food poisoning
<i>Enterococcus faecalis</i>	Urinary tract, wound, intestinal, and heart infections
<i>Listeria monocytogenes</i>	Lethal infection in newborns
<i>Mycobacterium tuberculosis</i>	Tuberculosis
<i>Neisseria meningitidis</i>	Meningitis and septicemia (brain membrane inflammation and blood poisoning)
<i>Streptococcus pyogenes</i>	Puerperal fever, scarlet fever, pharyngitis, impetigo, cellulitis, “flesh-eating bacteria”
<i>Treponema pallidum</i>	Syphilis
<i>Vibrio cholerae</i>	Cholera
<i>Yersinia pestis</i>	Plague
<b>Nonbacterial</b>	
<i>Brugia malayi</i> (a worm)	Elephantiasis (grossly enlarged lymph nodes)
<i>Entamoeba histolytica</i>	Intestinal infection
<i>Plasmodium falciparum</i>	Malaria
<i>Schistosoma mansoni</i>	Schistosomiasis
<i>Toxoplasma gondii</i>	Birth defects, opportunistic infection in AIDS
<i>Trypanosoma brucei</i>	African sleeping sickness
<i>Trypanosoma cruzi</i>	Chagas disease

system. This strategy enabled researchers to rapidly develop vaccines against severe acquired respiratory syndrome (SARS).

## Crowd Diseases

History provides clues to the complex and ever-changing relationships between humans and our pathogens. Because adaptive immunity responds to an environmental stimulus, epidemics often followed the introduction of a pathogen into a population that had not encountered it before.

When Europeans first explored the New World, they inadvertently brought bacteria and viruses to which their immune systems had adapted. The immune systems of Native Americans, however, had never encountered these pathogens. Many people died. Smallpox decimated the Aztec population in Mexico from 20 million in 1519, when conquistador Hernán Cortés arrived from Spain, to 10 million by 1521, when Cortés returned. By 1618,

the Aztec nation had fallen to 1.6 million. The Incas in Peru and northern populations were also dying of smallpox. When explorers visited what is now the southeast United States, they found abandoned towns where natives had died from smallpox, measles, pertussis, typhus, and influenza.

The diseases that so easily killed Native Americans are known as “crowd” diseases, because they arose with the spread of agriculture and urbanization and affect many people. Crowd diseases swept Europe and Asia as expanding trade routes spread bacteria and viruses along with silk and spices. Today air travel spreads crowd diseases.

Crowd diseases tend to pass from conquerors who live in large, intercommunicating societies to smaller, more isolated and susceptible populations, not vice versa. When Columbus arrived in the New World, the large populations of Europe and Asia had existed far longer than American settlements. In Europe and Asia, infectious

diseases had time to become established and for human populations to adapt to them. In contrast, an unfamiliar infectious disease can quickly wipe out an isolated tribe, leaving no one to give the illness to new invaders.

Most crowd diseases vanish quickly, for several reasons: vaccines or treatments may stop transmission; people may alter their behaviors to avoid contracting the infection; or the disease may kill before individuals can pass it on. Sometimes, we don’t know why a disease vanishes or becomes milder.

We may be able to treat and control newly evolving infectious diseases one at a time, with new drugs and vaccines. But the mutation process that continually spawns new genetic variants in microbe populations—resulting in evolution—means that new infectious diseases will continue to arise, and old ones to return or ravage new populations.

## Bioweapons

It may seem incomprehensible that anyone would ever use pathogens to intentionally harm people, but it is a sad fact of history—and the present—that such bioweapons exist. Biological weapons have been around since medieval warriors catapulted plague-ridden corpses over city walls to kill the inhabitants. During the French and Indian War, the British gave Native Americans blankets intentionally contaminated with secretions from smallpox victims. Although international law banned “germ warfare” in 1925, from 1932 until 1942 Japan field-tested bacterial bioweapons in rural China, killing thousands.

In 1973, the Soviet Union established an organization called Biopreparat. Thousands of workers in 50 facilities prepared anthrax bombs and other bioweapons under the guise of manufacturing legitimate drugs, vaccines, and veterinary products. Soviet bioweapons were even more lethal than their natural counterparts. Plague bacteria, for example, were genetically modified to resist sixteen antibiotics and to manufacture a protein that strips nerve cells of their fatty coats, adding paralysis to the list of natural symptoms.

Anthrax has continued to leave its mark on the history of bioweaponry. In 1979, an accident occurred in a Soviet city then



called Sverdlovsk. At Military Compound Number 19, a miscommunication among shift workers in charge of changing safety air filters caused the release of a cloud of dried anthrax spores over the city. Within weeks, more than 100 people died of anthrax. They were mostly young, healthy men who were outside on that Friday night and breathed in enough anthrax spores to cause the inhaled form of the illness. The government officially announced that the deaths were due to eating infected meat. Then workers sprayed water everywhere, reaerosolizing the spores and causing more infections. The deadline of inhalation anthrax is why health officials were so concerned when spores were mailed to a senator, media representatives, and others in 2001 in the United States. Several people died and more people showed immune responses to the exposures than had been thought at the time.

The symptoms of inhalation anthrax result from a toxin that consists of three proteins. One protein forms a barrel-like structure that binds to macrophages and admits the other two components of the

toxin. One of these components overloads signal transduction and impairs the cell's ability to engulf pathogens. The other toxin component breaks open macrophages, which release tumor necrosis factor and interleukins. Early symptoms of inhalation anthrax resemble influenza, but the victim rapidly suffers respiratory collapse.

In September 1992, then-president Boris Yeltsin officially halted bioweapon research in the former Soviet Union. Twenty years earlier, political leaders in London, Moscow, and Washington had signed the Biological Weapons Convention, an effort to prevent bioterrorism. Its protocols are being strengthened today.

In the United States, a small-scale bioweapons effort began in 1942. A facility at Fort Detrick in Frederick, Maryland, stored 5,000 bombs loaded with anthrax spores; a production facility for the bombs was located in Terre Haute, Indiana; and Mississippi and Utah had test sites. President Richard Nixon halted the program in 1969; he thought that conventional and nuclear weapons were a sufficient deterrent and defense.

Today bioweapons are again a threat. Such weapons have come far since the Japanese dropped porcelain containers of plague-ridden fleas over China. Today's bioterrorists not only know how to grow and dry pathogens, but how to control particle size to ease infection. In addition, genetic modification can alter the characteristics of a virus or bacterium intended for use as a weapon, making it even deadlier, or targeting specific types of victims.

## Key Concepts

1. Knowing the genome sequence of a pathogen can reveal how it evades the human immune system.
2. Crowd diseases happen when infectious agents are introduced into a population that hasn't encountered them before.
3. Bioterrorism is the use of pathogens—either in their natural state or genetically manipulated—to kill people.

## Summary

### 17.1 The Importance of Cell Surfaces

1. The cells and biochemicals of the immune system distinguish self from nonself, protecting the body against infections and cancer.
2. Most genetic effects on immunity are polygenic, but a few single genes have significant effects.
3. Patterns of cell surface proteins and glycoproteins determine blood types. An **antigen** is a molecule that elicits an immune response. A blood incompatibility occurs if a blood recipient manufactures **antibodies** against antigens in donor blood. Blood type systems include ABO and Rh.
4. **HLA** genes are closely linked on chromosome 6 and encode cell surface antigens that present foreign antigens to the immune system.

### 17.2 The Human Immune System

5. If a pathogen breaches physical barriers, the **innate immune response** produces the

redness and swelling of inflammation, plus complement, collectins, and cytokines. The response is broad and general.

6. The **adaptive immune response** is slower, specific, and has memory. This response is both humoral and cellular.
7. The **humoral immune response** begins when macrophages display foreign antigens near HLA antigens. This activates **T cells**, which activate **B cells**. The B cells, in turn, give rise to plasma cells and secrete specific antibodies. Some B cells give rise to memory cells.
8. An antibody is Y-shaped and made up of four polypeptide chains, two heavy and two light. Each antibody molecule has regions of constant amino acid sequence and regions of variable sequence.
9. The tips of the Y of each subunit form antigen binding sites, which include the more specific idiotypes that bind foreign antigens at their epitopes.
10. Antibodies bind antigens to form immune complexes large enough for other immune system components to detect and destroy.

Antibody genes are rearranged during early B cell development, providing instructions to produce a great variety of antibodies.

11. T cells carry out the **cellular immune response**. Their precursors, called thymocytes, are selected in the thymus to recognize self. Helper T cells secrete cytokines that activate other T cells and B cells. A helper T cell's CD4 antigen binds macrophages that present foreign antigens. Cytotoxic T cells release biochemicals that bore into and kill bacteria and also destroy cells covered with viruses.

### 17.3 Abnormal Immunity

12. Mutations in antibody or cytokine genes, or in genes encoding T cell receptors, cause inherited immune deficiencies. Severe combined immune deficiencies affect both branches of the immune system.
13. HIV binds to the coreceptors CD4 and CCR5 on macrophages and helper T cells, and, later in infection, triggers apoptosis of cytotoxic T cells. As HIV replicates, it mutates, evading immune attack.

Falling CD4 helper T cell numbers allow opportunistic infections and cancers to flourish. People who cannot produce a complete CCR5 protein resist HIV infection.

14. In an **autoimmune disease**, the body manufactures **autoantibodies** against its own cells. Autoimmunity may result from a virus that incorporates and displays a self antigen, from bacteria or cancer cells that have antigens that resemble self antigens, from unselected T cells, or from lingering fetal cells.
15. In susceptible individuals, allergens stimulate IgE antibodies to bind to mast cells, which causes the cells to release allergy mediators. Certain helper T cells

release selected cytokines. Allergies may be a holdover of past immune function.

## 17.4 Altering Immune Function

16. A **vaccine** presents a disabled pathogen, or part of one, to elicit a primary immune response.
17. Immunotherapy enhances or redirects immune function. **Monoclonal antibodies** are useful in diagnosing and treating some diseases because of their abundance and specificity. To create MABs, individual activated B cells are fused with cancer cells to form hybridomas. Cytokines are used to treat various conditions.
18. Transplant types include autografts (within oneself), isografts (between identical

twins), allografts (within a species), and xenografts (between species). A tissue rejection reaction occurs if donor tissue is too unlike recipient tissue.

## 17.5 A Genomic View of Immunity—The Pathogen's Perspective

19. Learning the genome sequences of pathogens can reveal how they infect, which provides clues to developing new treatments.
20. Crowd diseases spread rapidly through a population that has had no prior exposure, passed from members of a population that have had time to adapt to the pathogen.
21. Throughout history, people have used bacteria and viruses as weapons.

# Review Questions

1. Match the cell type to the type of biochemical it produces.

1. mast cell	a. antibodies
2. T cell	b. HLA class II genes
3. B cell	c. interleukin
4. macrophage	d. histamine
5. all cells with nuclei	e. interferon
6. antigen-presenting cell	f. heparin
	g. tumor necrosis factor
	h. HLA class I A, B, and C genes
2. Distinguish between
  - a. a T cell and a B cell.
  - b. innate and adaptive immunity.
  - c. a primary and secondary immune response.
  - d. a cellular and humoral immune response.
  - e. an autoimmune condition and an allergy.
  - f. an inherited and acquired immune deficiency.
3. What is the physical basis of a blood type? of blood incompatibility?
4. What would be the consequences of lacking
  - a. helper T cells?
  - b. cytotoxic T cells?
  - c. B cells?
  - d. macrophages?
5. State the function of each of the following immune system biochemicals:
  - a. complement proteins
  - b. collectins
  - c. antibodies
  - d. cytokines
6. Which components of the human immune response explain why we experience the same symptoms of an upper respiratory infection (a “cold”) when many different types of viruses can cause these conditions?
7. What does HIV do to the human immune system?
8. What are the dangers of a bone marrow transplant being too different from the recipient’s tissues? too similar?
9. Cite three reasons why developing a vaccine against HIV infection has been challenging.
10. It was once said that thymocytes are “educated” in the thymus, meaning that immature T cells are somehow “taught” to recognize self cell surfaces and refrain from attack. This is not exactly what happens. Why?
11. What part do antibodies play in allergic reactions and in autoimmune disorders?
12. Explain how the immune system can respond to millions of different nonself antigens, if there are only a few hundred antibody genes.
13. Cite two explanations for why autoimmune disorders are more common in females.
14. How do each of the following illnesses disturb immunity?
  - a. graft-versus-host disease
  - b. SCID
  - c. scleroderma
  - d. AIDS
  - e. hayfever
15. Why is a deficiency of T cells more dangerous than a deficiency of B cells?
16. What do a plasma cell and a memory cell descended from the same B cell have in common? How do they differ?
17. Why is a polyclonal antibody response valuable in the body, but a monoclonal antibody valuable as a diagnostic tool?
18. State how each of the following alters immune system functions:
  - a. a vaccine
  - b. an antibiotic drug
  - c. a cytokine-based drug
  - d. an antihistamine drug
  - e. a transplant

# Applied Questions

1. A man is flown to an emergency room of a major medical center, near death after massive blood loss in a car accident. There isn't time to match blood types, so the physician orders type O negative blood. Why did she order this type of blood?
2. Rasmussen's encephalitis causes 100 or more seizures a day. Affected children have antibodies that attack brain cell receptors that normally bind neurotransmitters. Is this condition most likely an inherited immune deficiency, an adaptive immune deficiency, an autoimmune disorder, or an allergy? State a reason for your answer.
3. Allergy to a protein in peanuts can cause anaphylactic shock. An experimental vaccine consists of the gene encoding this protein, wrapped in an edible carbohydrate, so it can be eaten and stimulate production of protective antibodies in the small intestine. When this vaccine was fed to rats who have a peanut allergy, their blood showed lowered levels of IgE, but increased levels of IgG. Also, their bowel movements contained higher than usual levels of IgA. Is the vaccine working? How can you tell?
4. In the TV program *House*, a talented physician and his staff confront difficult-to-diagnose medical cases. They often have to hypothesize whether symptoms are due to an infection, allergy, poison, autoimmunity, or genetic disease. Discuss how these alternatives might be distinguished.
5. What type of information is needed to test the hygiene hypothesis?
6. What might be the effect on health of a deletion that removes most of the V genes?
7. In people with a certain HLA genotype, a protein in their joints resembles an antigen on the bacterium that causes Lyme disease. This infection is transmitted in a tick bite and causes flulike symptoms and joint pain (arthritis). When these individuals become infected, their immune systems attack the bacteria and their joints. Explain why antibiotics treat the early phase of the disease, but not the arthritis.
8. Even in deadly infectious diseases, such as plague and Ebola hemorrhagic fever, a small percentage of the human population survives. Suggest two mechanisms based on immune system functioning that can account for their survival.
9. A person exposed for the first time to Coxsackie virus develops a painful sore throat. How is the immune system alerted to the exposure to the virus? When the person encounters the virus again, why doesn't she develop symptoms?
10. A young woman who has aplastic anemia will soon die as her lymphocyte levels drop sharply. What type of cytokine might help her?
11. In Robin Cook's novel *Chromosome Six*, a geneticist places a portion of human chromosome 6 into fertilized ova from bonobos (pygmy chimps). The bonobos that result are used to provide organs for transplant into specific individuals. Explain how this technique would work.
12. Suggest ways that local, state, and federal governments can prepare to handle a bioterrorism attack.
13. Is the heritability of SCID likely to be higher or lower than that for an allergy? Why?

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 17**, and **Web Activities** to find the website links needed to complete the following activities.

14. Many websites describe products (food supplements) that supposedly "boost" immune system function. Very often, the descriptions are vague, use meaningless jargon or buzzwords, or contain misinformation. Locate such a website and identify claims that are unclear, deceptive, or incorrect. Alternatively, identify a claim that is consistent with the description of immune system function in this chapter.
15. Go to the Blood Book website. This site explains human blood groups; use it to try to answer the following questions.
  - a. Which blood group is capable of being the most diverse in a population?
  - b. Why has classification of human blood types been so confusing?
  - c. In predicting blood types of future offspring, why would it be important to know whether the genes encoding different blood group antigens, or the enzymes that make their synthesis possible, are linked or unlinked?

## Case Studies and Research Results

16. African Americans are at higher risk of developing conditions associated with a too-vigorous inflammatory response (heart attack, diabetes, stroke, and kidney disease) than others. To see whether this tendency is inherited, researchers examined variants of several genes whose protein products regulate cytokines (interleukins and tumor necrosis factor). The investigators compiled the genetic information for 179 African American women and 396 white women who delivered healthy babies at a Boston hospital between 1997 and 2001. The African Americans were much more likely to have genetic profiles indicating increased inflammation than the white women.
  - a. From this information, what would you conclude about the causes of the increased risk for inflammatory conditions among African Americans?
  - b. What other factors besides an association with skin color might contribute to the increased risk?
  - c. Why might certain alleles be more common in one population?
  - d. Design an experiment to test whether some other factor, such as economic status or whether one lives in a city or rural area, contributes to elevated risk of developing inflammatory disorders.
17. State whether each of the following situations involves an autograft, an isograft, an allograft, or a xenograft.
  - a. A man donates part of his liver to his daughter, who has a liver damaged by cystic fibrosis.
  - b. A woman with infertility receives an ovary transplant from her identical twin.
  - c. A man receives a heart valve from a pig.
  - d. A woman who has had a breast removed has a new breast built using her fatty thigh tissue.
18. Mark and Louise are planning to have their first child, but they are concerned because they think that they have an Rh incompatibility. He is Rh<sup>-</sup> and she is Rh<sup>+</sup>. Will there be a problem? Why or why not?



# A Second Look

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1. RA is about equally likely to affect both members of MZ (identical) twin pairs as it is DZ (fraternal) twin pairs. Explain why this observation indicates that RA is not inherited.
2. How can gene expression differ among people with RA, if it is not a single-gene disorder?
3. Suggest a study that might be conducted to identify nongenetic factors that increase the risk of developing RA.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

Stiff person syndrome

A vanishing twin helps an athlete



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Genetics of Cancer

## CHAPTER CONTENTS

- 18.1 **Cancer Is Genetic, But Usually Not Inherited**
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## MICROARRAYS ILLUMINATE THYROID CANCER

I never thought I would care much about the cells of my thyroid gland. That changed on August 4, 1993, when my physician, looking at me from across a room, said, “What’s that lump in your neck?”

Soon after, a specialist stuck six thin needles into the lump to sample thyroid cells for testing, telling me that 99 percent of thyroid lumps are not cancerous. However, when he approached with a seventh needle for a sample for a study on something called *p53*, I began to worry, because *p53* is a gene associated with cancer. When the specialist called early on a Monday morning, I knew I was among the unlucky 1 percent. I had papillary thyroid cancer, which accounts for 80 percent of cases and is easily treated with surgery and radioactive iodine. But when I was on the operating table, the surgeon did not think my lump looked like a papillary tumor. Off it went to the pathology lab, while I waited on the table. The results: I had two tumors, one papillary, one follicular. Treatment was successful.

Had I developed thyroid cancer today, I might not have had to wait on an operating table while a pathologist examined my cells for the telltale distinctions between tumor types. DNA microarrays can now highlight five key genes that are expressed differently in papillary and follicular thyroid cancers. My physicians would have known, before surgery, the genetic nature of my tumors. This approach is very valuable for cancer in which treatment differs depending upon the genetic profiles of the cells, such as breast or prostate cancers.



I had no symptoms of my thyroid cancer, and did not even notice the subtle, yet egg-sized swelling in my neck.

Cancer has been part of human existence for eons. Egyptian mummies from 3000 B.C., show evidence of cancerous tumors, and by 1600 B.C., the Egyptians were attempting to treat cancer. Papyrus illustrate them cutting or burning off growths, and using more inventive treatments for less obvious tumors. A remedy for uterine cancer, for example, introduced fresh ground dates mixed with pig's brain into the vagina!

By 300 B.C., Hippocrates had described several types of tumors, and coined the term “cancer” to describe the crablike shape of a tumor invading normal tissue. He attributed cancer to a buildup of black bile; others blamed it on fermenting lymph, injury, irritation, or simply “melancholia.” Today we know that the collection of diseases called cancer reflects a profound derangement of the cell cycle that can be set into motion by environmental factors. Sequences of mutations in somatic cells underlie the progression of cancer as it spreads.

Cancer has or will affect one in three of us. Diagnosis and treatment are becoming increasingly individualized, thanks largely to genetic and genomic approaches to describing cancer cells.

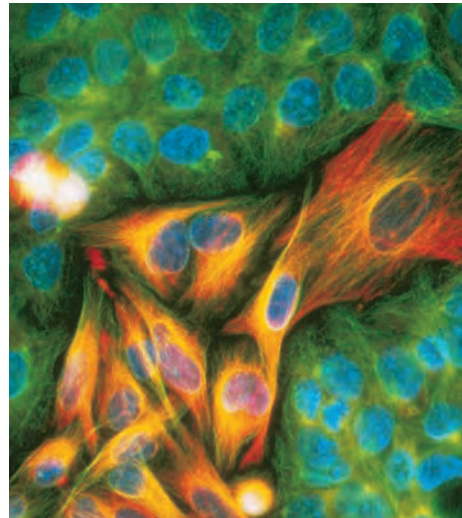
## 18.1 Cancer Is Genetic, But Usually Not Inherited

Cancer is a complication of being a many-celled organism. Our specialized cells must follow a schedule of mitosis—the cell cycle—so that organs and other body parts either grow appropriately during childhood, stay a particular size and shape in an adult, or repair damage by replacing tissue. If a cell in solid tissue escapes normal controls on its division rate, it forms a growth called a tumor (**figure 18.1**). In the blood, such a cell divides to take over the population of blood cells. A tumor is benign if it grows in place but does not spread into, or “invade,” surrounding tissue; a tumor is cancerous, or malignant, if it infiltrates nearby tissue. A malignant tumor also sends parts of itself into the bloodstream or lymphatic vessels, either of which transports it to other areas, where the cancer cells “seed” the formation of new tumors. The process of spreading is termed **metastasis**, which means “not standing still.”

Cancer is a group of disorders that arise from alterations in genes. Only about 10 percent of cases are inherited as single-gene



a.



b.

**Figure 18.1 Cancer cells stand out.** (a) A melanoma is a cancer of the pigment-producing cells (melanocytes) in the skin. It may have any or all of four characteristics, abbreviated ABCD: it is asymmetric, has borders that are irregular, color variations, and a diameter of more than 5 millimeters. (b) Stains and dyes reveal cancer at the cellular level. These melanoma cells stain orange. The different staining characteristics of cancer cells reflect differences in gene expression patterns between the normal and cancerous states.

disorders, in which the faulty instructions are in every cell. More often, mutations in cancer-causing genes occur in a few somatic cells over a lifetime. Cancer is usually a genetic disease at the cellular level, but not at the whole-body level.

Probably combinations of particular gene variants sum to increase the risk of cancer, perhaps by making cells more sensitive to environmental factors that affect the cell cycle. As a result, cancer may “run in families” yet not follow a single-gene pattern of inheritance. Cancer often takes years to develop, as a sequence of genes mutate in the affected tissue. Then, the cells whose mutations enable them to divide more

often than others gradually take over the tissue. At the same time, changes at the gene expression level fuel the disease process. Even though a cancer may not spread for years, mutations or changes in gene expression that indicate that it will do so can occur early in the course of illness.

Cancer wasn’t always considered a genetic phenomenon. When President Richard Nixon declared a “war on cancer” in 1971, the targets were radiation, viruses, and chemicals. These agents actually cause cancer by interfering with the precise genetic controls of cell division.

An early hint at the genetic nature of cancer was the observation that most substances known to be carcinogens (causing cancer) are also mutagens (damaging DNA). Researchers first discovered genes that could cause cancer in 1976. In the 1980s and 1990s, searches for cancer-causing genes began with rare families that had many young members who had the same type of cancer and specific unusual chromosomes. Then the search focused on genes in the identified region whose protein products could affect cell cycle control. This approach led to the discovery of more than 100 **oncogenes**. An oncogene causes cancer when inappropriately activated. These family studies also identified more than 30 **tumor suppressor** genes, which cause cancer when they are deleted or inactivated. The normal function of a tumor suppressor gene is to keep the cell cycle running at the normal rate for a particular cell type.

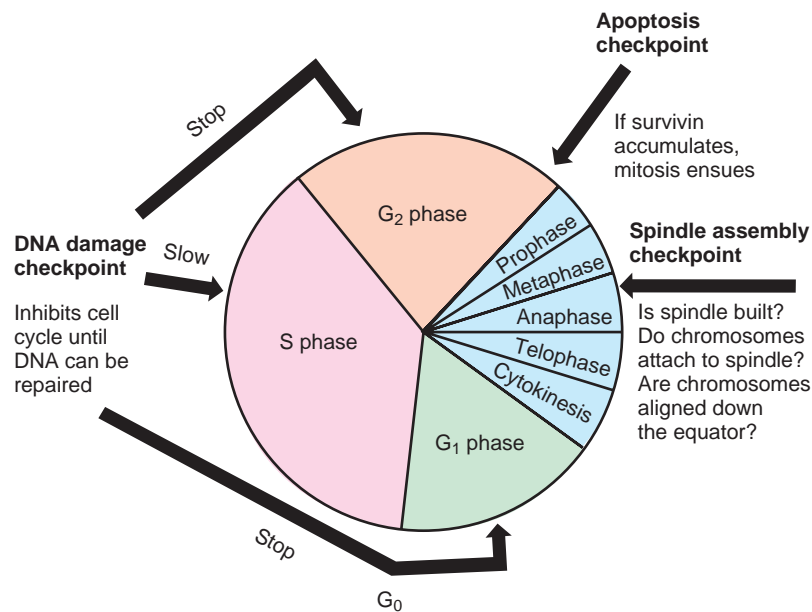
In addition to oncogenes and tumor suppressors, changes in gene expression accompany cancer. DNA microarrays highlight mutations and patterns of gene expression that paint “molecular portraits” of the disease. These views are making it possible to recognize subtypes of cancers affecting the same cell types, as the opener to chapter 11 discusses for leukemia. The subtypes explained why the prevailing treatment did not work for some young patients.

## Loss of Cell Cycle Control

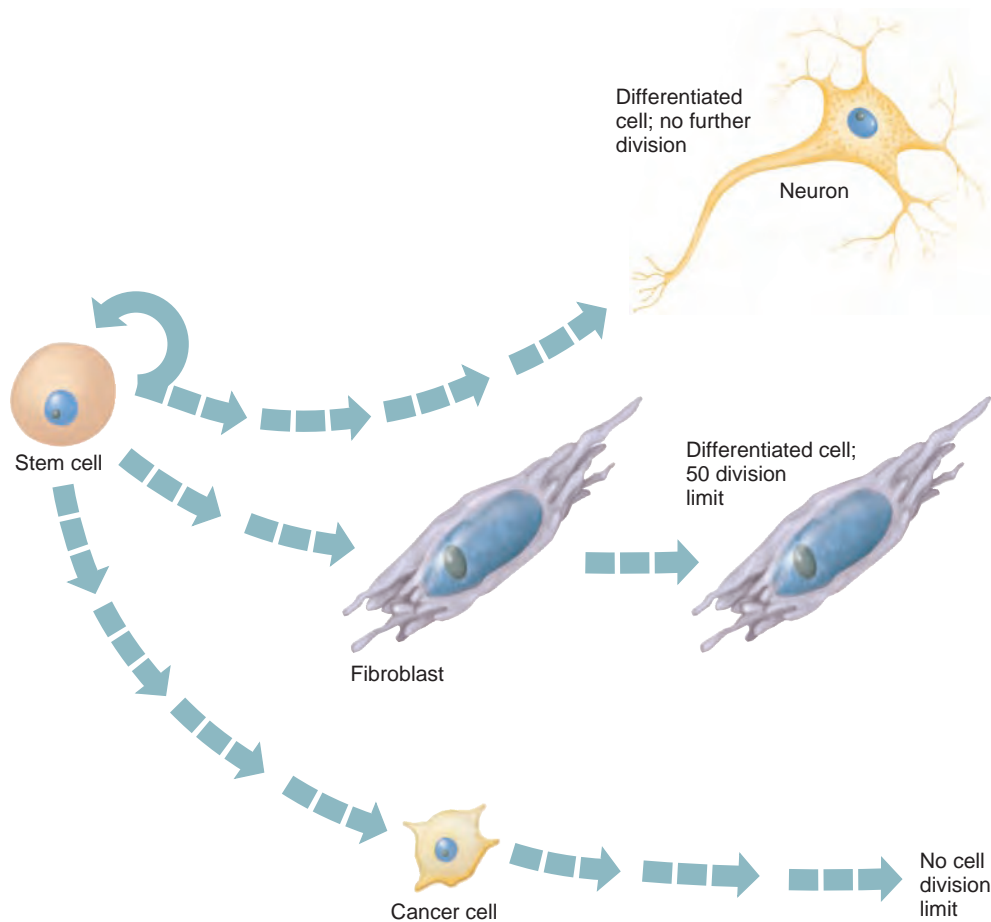
Cancer is a consequence of cell cycle disruption. **Figure 18.2** repeats the cell cycle diagram from chapter 2. It begins when a cell divides more frequently, or more times, than the normal cell type it descended from (**figure 18.3**).

The timing, rate, and number of mitoses a cell undergoes depend on protein growth





**Figure 18.2 Cell cycle checkpoints.** Checkpoints ensure that mitotic events occur in the correct sequence. Many types of cancer result from faulty checkpoints.



**Figure 18.3 Cancer sends a cell down a pathway of unrestricted cell division.** Cells may be terminally differentiated and no longer divide, such as a neuron, or differentiated yet still capable of limited cell division, such as a fibroblast (connective tissue cell). Cancer cells either lose specializations or never specialize and divide unceasingly, ignoring the 50-or-so division “Hayflick limit for cultured cells.” (Arrows represent some cell divisions; not all daughter cells are shown.)

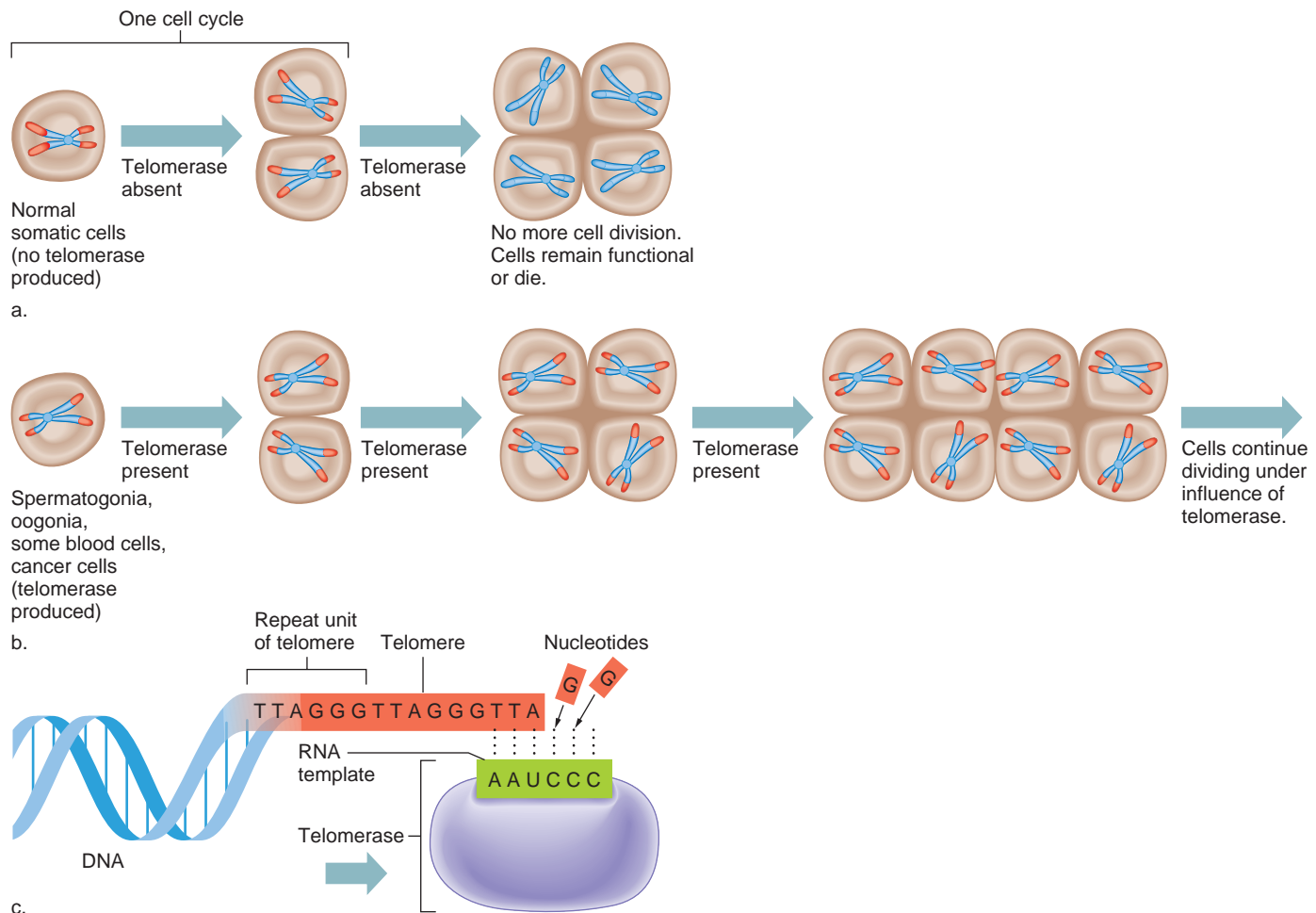
factors and signaling molecules from outside the cell, and on transcription factors from within. Because these biochemicals are under genetic control, so is the cell cycle. Cancer cells probably arise often, because mitoses are so frequent that an occasional cell escapes control. However, the immune system destroys most cancer cells after recognizing tumor-specific antigens on their surfaces.

The discovery of the checkpoints that control the cell cycle revealed how cancer can begin. A mutation in a gene that normally halts or slows the cell cycle can lift the constraint, leading to inappropriate mitosis. Failure to pause long enough to repair DNA can allow a mutation in an oncogene or tumor suppressor gene to persist.

Loss of control over telomere length may also contribute to cancer by affecting the cell cycle. Recall that telomeres, or chromosome tips, protect chromosomes from breaking. Human telomeres consist of the DNA sequence TTAGGG repeated thousands of times. The repeats are normally lost from the telomere ends as a cell matures, from 15 to 40 nucleotides per cell division. The more specialized a cell, the shorter its telomeres. The chromosomes in skin, nerve, and muscle cells, for example, have short telomeres. Chromosomes in a sperm cell or oocyte, however, have long telomeres. This makes sense—as the precursors of a new organism, gametes must retain the capacity to divide many times.

Gametes keep their telomeres long thanks to an enzyme, telomerase, that is a complex of RNA and protein. Part of the RNA—the sequence AAUCCC—serves as a template for the 6-DNA-base repeat TTAGGG that builds telomeres (**figure 18.4**). Telomerase moves down the DNA like a zipper, adding six “teeth” (bases) at a time.

In normal, specialized cells, telomerase is turned off, and telomeres shrink, signaling a halt to cell division when they reach a certain size. In cancer cells, telomerase is turned back on. Telomeres extend, and this releases the normal brake on rapid cell division. As daughter cells of the original abnormal cell continue to divide uncontrollably, a tumor forms, grows, and may spread. Usually the longer the telomeres in cancer cells, the more advanced the disease. However, turning on telomerase production in a cell is not sufficient in itself to cause cancer. Many other things must go wrong for cancer to begin.



**Figure 18.4 Telomeres.** (a) In normal somatic (nonsex) cells, telomeres shorten with each cell division because the cells do not produce telomerase. When the telomeres shrink to a certain point, the cell no longer divides. (b) Sperm-generating cells, blood cells, and cancer cells produce telomerase and continually extend their telomeres, resetting the cell division clock. (c) Telomerase contains RNA, which includes a portion (the nucleotide sequence AAUCCC) that acts as a template for the repeated DNA sequence (TTAGGG), which forms the telomere.

## Inherited Versus Sporadic Cancer

Although cancer genes were discovered in families with inherited cancers, most cancers are sporadic, which means that the causative mutations occur only in cells of the affected tissue. These are **somatic mutations**, because they occur in nonsex cells. A sporadic cancer may result from a single dominant mutation or from two recessive mutations in the same gene. The cell harboring the mutation loses control of its cell cycle, divides continuously, and a tumor forms and grows.

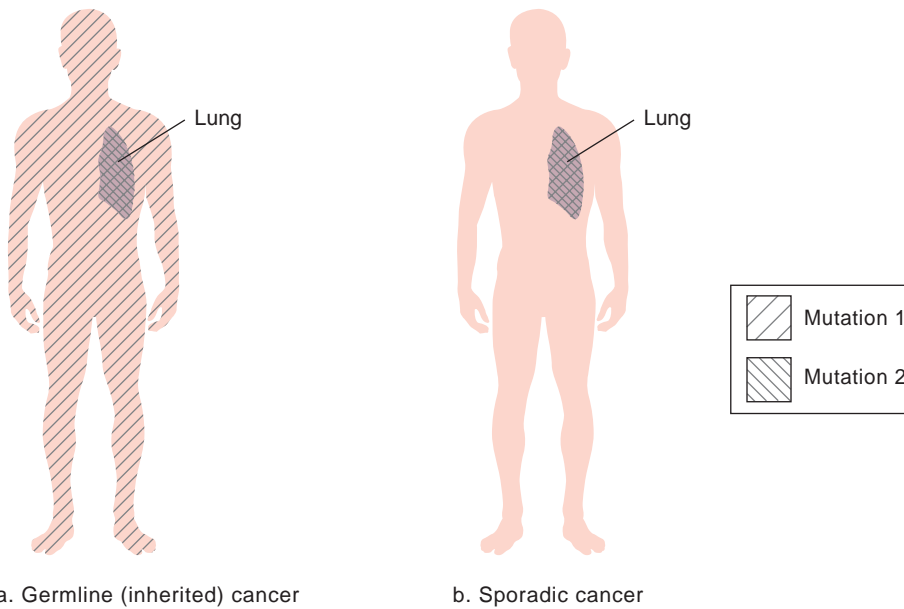
Susceptibility to developing a sporadic cancer is *not* directly passed on to future generations because the gametes do not carry the mutant allele or alleles. In contrast are **germline mutations**, in which cancer susceptibility is directly passed to future generations

because the mutations are in every cell, including gametes. Cancer develops when a second mutation occurs in a somatic cell in the affected body part (**figure 18.5**).

Germline mutations may explain why some heavy smokers develop lung cancer, but many do not; the unlucky ones may have inherited a susceptibility allele in every cell. Years of exposing lung tissue to the carcinogens in smoke eventually cause a mutation in a tumor suppressor gene or oncogene of a lung cell, giving it a proliferative advantage. Without the susceptibility gene, two such somatic mutations are necessary to trigger the cancer. This, too, can be the result of an environmental insult, but it takes longer for two events to occur than one. Germline cancers are rare, but they have high penetrance and tend to strike earlier in life than sporadic cancers.

## Key Concepts

1. Cancer is genetic, but not necessarily inherited.
2. Single genes (oncogenes and tumor suppressors), when mutant, can cause cancer. Cancer cells have different gene expression profiles compared to the cells from which they descend.
3. Cancer is caused by a loss of cell division control. Implicated genes encode growth factors, transcription factors, or telomerase.
4. Most cancer mutations occur in somatic cells.
5. Cancer may develop when an environmental trigger mutates a somatic cell (sporadic) or when a somatic mutation compounds an inherited susceptibility (germline).



**Figure 18.5 Germline versus sporadic cancer.** (a) In germline cancer, every cell has one gene variant that increases cancer susceptibility, and a second mutation occurs in a cell of the affected tissue. This type of predisposition to cancer is inherited as a single-gene trait. (b) A sporadic cancer forms when a dominant mutation occurs in a somatic cell or two recessive mutations occur in the same gene in the same somatic cell. An environmental factor, such as exposure to radiation or a chemical, can cause the somatic mutations that cause cancer. Note that each lung has undergone both mutations 1 and 2.

## 18.2 Characteristics of Cancer Cells

Cell division is rigorously controlled. Whether a cell divides or stops dividing and whether it differentiates depends upon signals from surrounding cells. A cancer cell simply stops “listening” to those signals.

Cancer cells can divide continuously if given sufficient nutrients and space. Cervical cancer cells of a woman named Henrietta Lacks, who died in 1951, vividly illustrate the hardiness of these cells. Her cells persist today as standard cultures in many research laboratories. These “HeLa” cells divide so vigorously that when they contaminate cultures of other cells they soon take over.

Cells vary greatly in their capacity to divide. Cancer cells divide more frequently or more times than the cells from which they arise. Yet even the fastest-dividing cancer cells, which complete mitosis every 18 to 24 hours, do not divide as often as some cells in a normal human embryo do. Still, some cancers grow alarmingly fast. The smallest detectable fast-growing tumor is half a centimeter in diameter and can contain a billion cells. These cells divide, producing a million or so new cells in an

hour. If 99 percent of the tumor’s cells are destroyed, 10 million are left to proliferate. Other cancers develop over years. A tumor grows more slowly at first because fewer cells divide. By the time the tumor is the size of a pea—when it is usually detectable—billions of cells are actively dividing. A cancerous tumor eventually grows faster than surrounding tissue because a greater proportion of its cells is dividing.

A cancer cell looks different from a normal cell. It is rounder because it does not adhere to surrounding normal cells as strongly as other cells do. Because the plasma membrane is more fluid, different substances cross it. A cancer cell’s surface may sport different antigens than are on other cells or different numbers of antigens that are also on normal cells. The “prostate specific antigen” (PSA) blood test that indicates increased risk of prostate cancer, for example, detects elevated levels of this protein that may come from cancer cells.

When a cancer cell divides, both daughter cells are cancerous, since they inherit the altered cell cycle control. Therefore, cancer is said to be heritable because it is passed from parent cell to daughter cell. A cancer is also transplantable. If a cancer cell is injected

into a healthy animal of the same species, it will proliferate there.

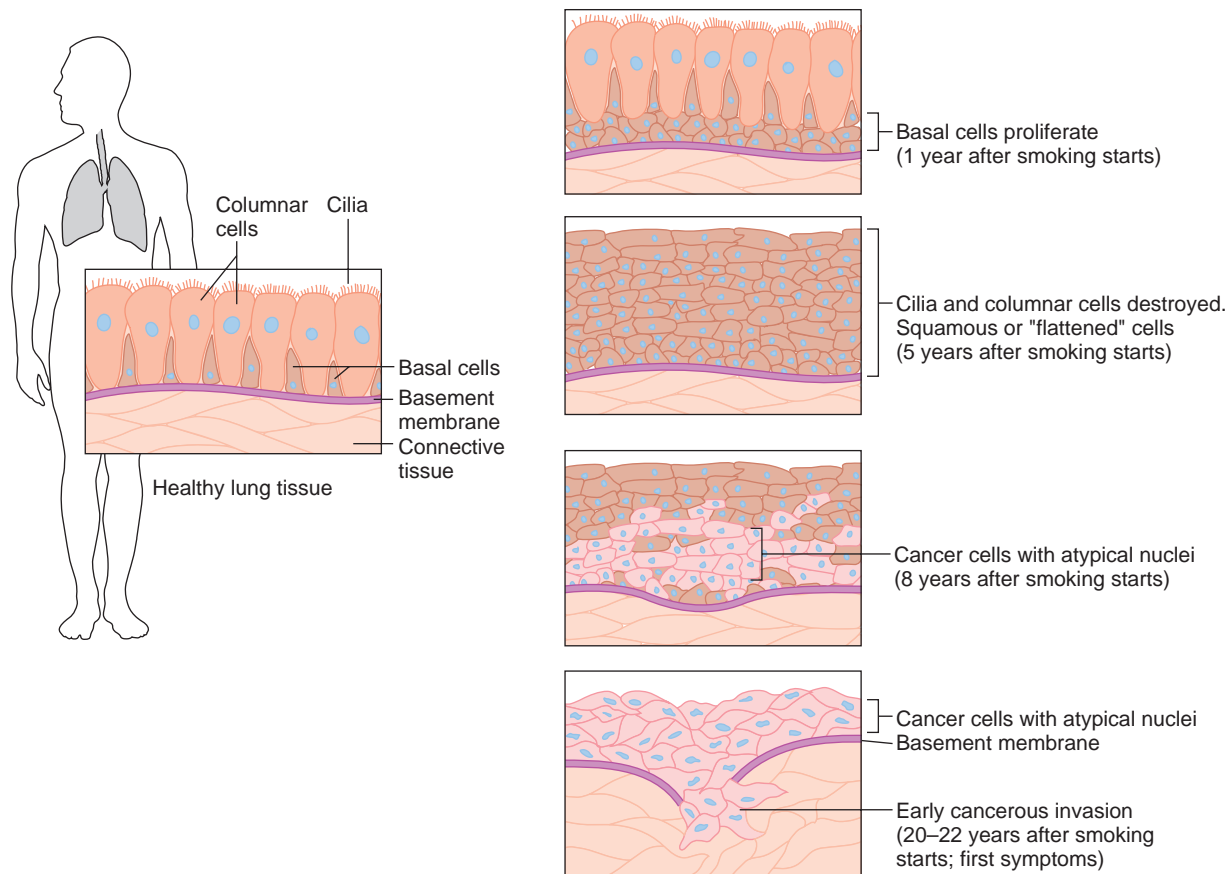
A cancer cell is **dedifferentiated**, which means that it is less specialized than the normal cell types near it that it might have descended from. A skin cancer cell, for example, is rounder and softer than the flattened, scaly, healthy skin cells above it in the epidermis, more like a stem cell in both appearance and division rate. Cancer cell growth is also unusual. Normal cells placed in a container divide to form a single layer; cancer cells pile up on one another. In an organism, this pileup would produce a tumor. Cancer cells that grow all over one another are said to lack contact inhibition—they do not stop dividing when they crowd other cells.

Cancer cells have surface structures that enable them to squeeze into any space, a property called invasiveness (**figure 18.6**). They anchor themselves to tissue boundaries, called basement membranes, where they secrete enzymes that cut paths through healthy tissue. Unlike a benign tumor, an invasive malignant tumor grows irregularly, sending tentacles in all directions.

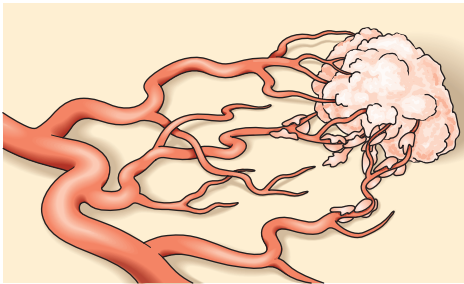
Cancer cells eventually reach the bloodstream or lymphatic vessels, which take them to other parts of the body—unless treatment stops the disease process. The traveling cancer cells settle into new sites—this is metastasis. Once a tumor has grown to the size of a pinhead, interior cancer cells respond to the oxygen-poor environment by secreting a protein, called vascular endothelial growth factor (VEGF). It stimulates nearby capillaries (the tiniest blood vessels) to sprout new branches that extend toward the tumor, bringing in oxygen and nutrients and removing wastes. This growth of new capillary extensions is called **angiogenesis**, and it is critical to a cancer’s growth and spread. Capillaries may snake into and out of the tumor (**figure 18.7**). Cancer cells wrap around the blood vessels and creep out upon this scaffolding, invading nearby tissue. In addition to attracting their own blood supply, cancer cells may also secrete hormones that encourage their own growth. This is a new ability because the cells they descend from do not produce these hormones.

Once cancer cells move to a new body part, the disease has metastasized. The DNA of secondary tumor cells often mutates, and chromosomes may break or rearrange.





**Figure 18.6 Cancers take many years to spread.** Lung cancer due to smoking begins with irritation of the lining tissue in respiratory tubes (bronchial epithelium). Ciliated cells die (but can be restored if smoking ceases), basal cells divide, and then, if the irritation continues, cancerous changes may appear.



**Figure 18.7 Angiogenesis nurtures a tumor.** Cells starved for oxygen deep within a tumor secrete vascular endothelial growth factor (VEGF), which stimulates nearby capillaries to extend branches toward a tumor. A class of drugs treats cancer by blocking angiogenesis in tumors.

Many cancer cells are aneuploid. The metastasized cancer thus becomes a new genetic entity that may resist treatments that were effective against most cells of the original tumor. Because gene expression patterns

**Table 18.1**

### Characteristics of Cancer Cells

Oilier, less adherent  
Loss of cell cycle control  
Heritable  
Transplantable  
Dedifferentiated  
Lack contact inhibition  
Induce local blood vessel formation (angiogenesis)  
Invasive  
Increased mutation rate  
Can spread (metastasize)

associated with metastasis are detectable early, new cancer treatments may actually prevent metastasis.

**Table 18.1** summarizes the characteristics of cancer cells.

## Key Concepts

1. Cancer occurs when cells divide faster or more times than normal.
2. Cancer cells are heritable, transplantable, and dedifferentiated. They lack contact inhibition, cutting through basement membranes.
3. A cancerous growth is invasive and can metastasize and stimulate angiogenesis, spreading farther.

## 18.3 Origins of Cancer Cells

Mutations that turn a cell cancerous are only a first step in the disease process. The degree to which the cell in which cancer begins is specialized, and the location of that cell in a tissue, are factors that influence whether or not disease develops.

At a cellular level, at least four situations can lead to cancer:

- activation of stem cells that produce cancer cells
- dedifferentiation
- increase in the proportion of a tissue that consists of stem or progenitor cells
- faulty tissue repair.

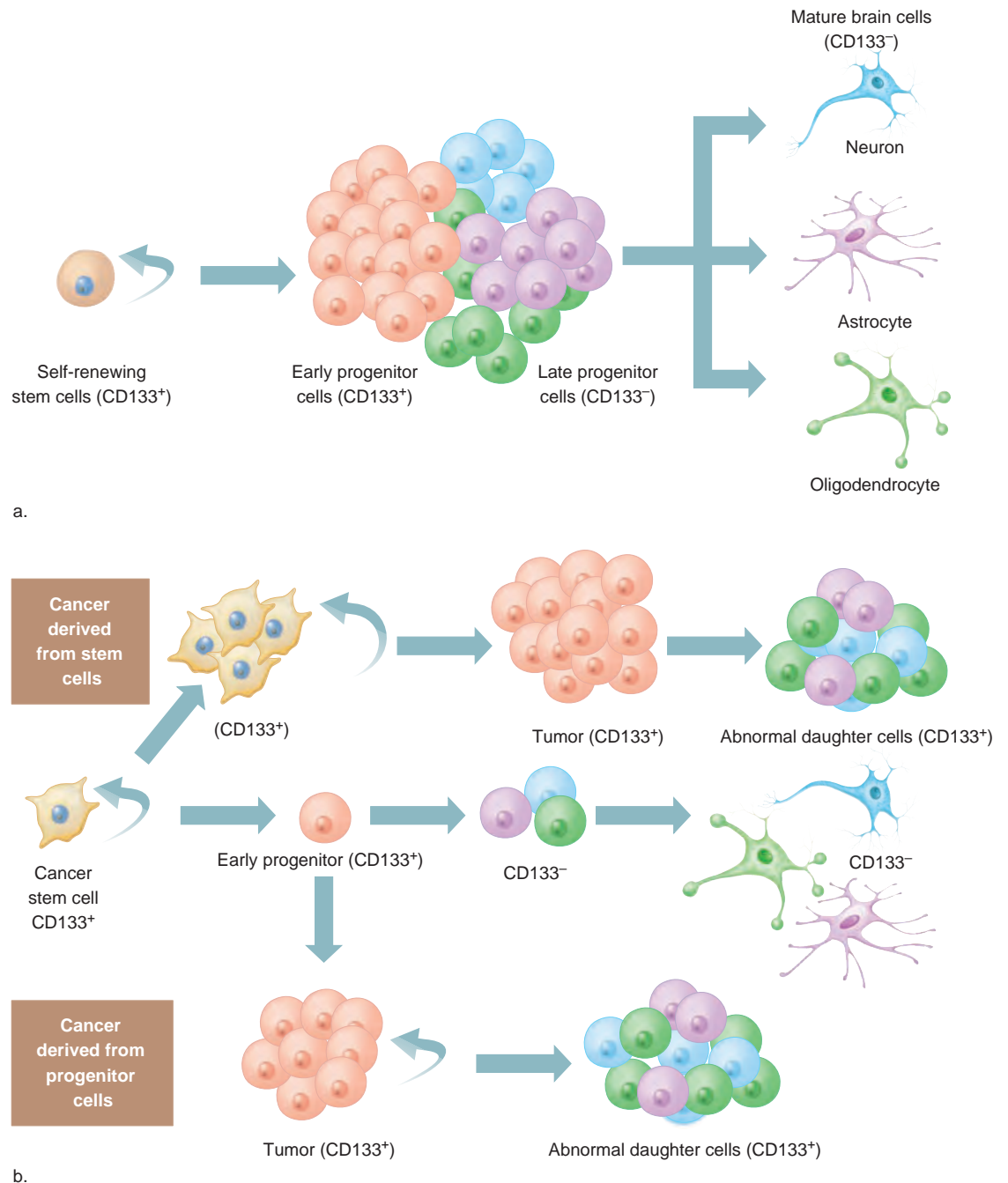
Most cancer cells are more specialized than stem cells, but considerably less specialized than the differentiated cells near them in a tissue (see figures 2.22 and 2.23). From which does the cancer cell arise? A cancer cell may descend from a stem cell that yields slightly differentiated daughter cells that retain the capacity to self-renew, or a cancer cell may arise from a specialized cell that loses some of its features and can divide. Certain stem cells, called **cancer stem cells**, veer from normal development and produce both cancer cells and abnormal specialized cells. Cancer stem cells are found in cancers of the brain, blood, and epithelium (lining tissues such as those in the breast, colon, and prostate).

**Figure 18.8** illustrates how cancer stem cells may cause brain tumors. In (a), as cancer stem cells give rise to progenitors and then differentiated cells (neurons, astrocytes, and oligodendrocytes), a cell surface molecule called CD133 is normally lost (designated  $CD133^-$ ) at the late progenitor stage. In contrast, in (b), cancer cells retain the molecule (designated  $CD133^+$ ). Some progenitor cells that descend from a cancer stem cell can relentlessly divide, and they ultimately accumulate, forming a brain tumor.

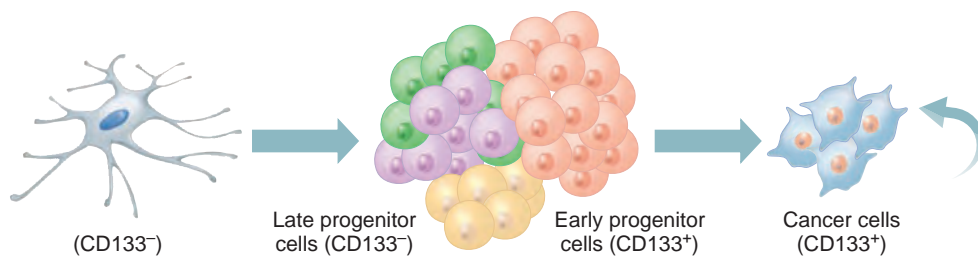
Another route to cancer may be cells that lose some of their distinguishing characteristics as mutations occur when

they divide, or they may begin to express “stemness” genes that override signals to remain specialized (**figure 18.9**). Whatever

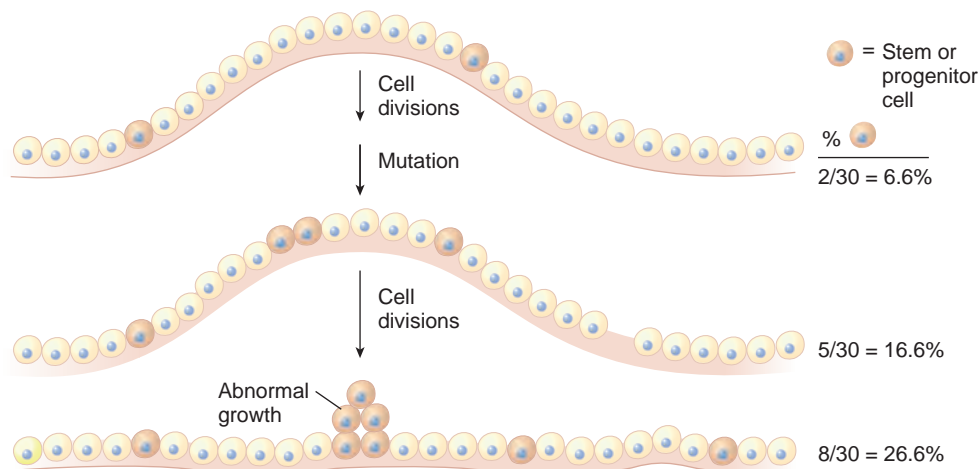
the mechanism, the result is dedifferentiation. So far experiments have not captured the exact moment when a cell both loses



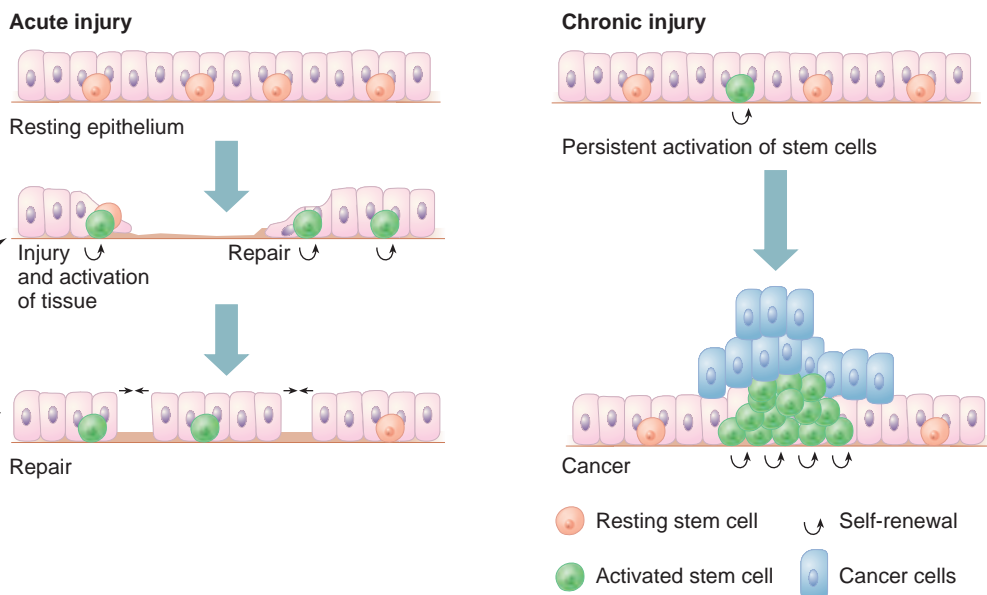
**Figure 18.8 Cancer stem cells.** (a) In the developing brain, stem cells divide to self-renew and give rise to early progenitor cells, which in turn divide to yield late progenitor cells. These late progenitor cells lose the CD133 cell surface marker, and they divide to give rise to daughter cells that specialize as neurons or two types of supportive cells, astrocytes or oligodendrocytes. (b) A cancer stem cell can divide to self-renew and give rise to a cancer cell, which in turn can also spawn abnormal daughter cells. Some early progenitors give rise to normal differentiated cells. Sometimes the cancer-causing mutations occur in the cancer stem cell-derived early progenitor cell. In this case, the early progenitors form the tumor, which may spawn some abnormal daughter cells. Note that stem cells, cancer stem cells, early progenitor cells, and abnormal daughter cells all have the  $CD133^+$  marker, but the differentiated cells do not.



**Figure 18.9 Dedifferentiation reverses specialization.** Mutations in a differentiated cell could reactivate latent “stemness” genes, giving the cell greater capacity to divide while causing it to lose some of its specializations. These are two of the defining characteristics of cancer.



**Figure 18.10 Shifting the balance in a tissue toward cells that divide.** If a mutation renders a differentiated cell able to divide to yield other cells that frequently divide, then over time these cells may take over, forming an abnormal growth.



**Figure 18.11 Too much repair may trigger tumor formation.** If epithelium is occasionally damaged, resting stem cells can become activated and divide to fill in the tissue. If injury is chronic, the persistent activation of stem cells to renew the tissue can veer out of control, fueling an abnormal growth.

specializations and becomes able to continually divide. However, researchers have identified a biochemical, named “reversine,” that can stimulate differentiated cells to divide and give rise to progenitor cells in mice. Reversine may play a role in the dedifferentiation of cancer cells.

Another possible origin of cancer may be a loss of balance at the tissue level in favor of cells that can divide continually or frequently—like a population growing faster if more of its members are of reproductive age. Consider a tissue that is 5 percent stem cells, 10 percent progenitors, and 85 percent differentiated cells. If a mutation, over time, shifts the balance in a way that creates more stem and progenitor cells, the extra cells pile up, and a tumor forms (**figure 18.10**).

Uncontrolled tissue repair may cause cancer (**figure 18.11**). If too many cells divide to fill in the space left by injured tissue, and those cells keep dividing, an abnormal growth may result.

With so many millions of cells undergoing so many error-prone DNA replications, and so many ways that cancer can arise, it perhaps isn’t surprising that cancer is so common. Yet most of the time, the immune system vanquishes a cancer before it progresses very far.

## Key Concepts

1. Cancer stem cells produce cancer cells and abnormal specialized cells.
2. Dedifferentiation might occur through mutation or overexpression of “stemness” genes.
3. Upsetting the balance of stem and progenitor to differentiated cells can cause cancer as excess, fast-dividing cells accumulate.

## 18.4 Cancer Genes

Discovering cancer genes is much like identifying other single genes that cause disease—it is a narrowing down of possibilities. Consider the recent identification of a gene that causes pancreatic cancer. It encodes a protein called palladin. Clues to the genetic cause of this rare cancer, which is familial in about 10 percent of cases, came from “family X,” in which



18 members over four generations have had either the cancer or precancerous lesions in the pancreas. Researchers identified a small sequence of chromosome 4, home to 243 known genes, as common to the affected relatives but not the others. Next, the researchers compared mRNA from affected pancreas cells to corresponding mRNAs from healthy family members and also to those of unrelated people with pancreatic cancer. The mRNAs for palladin stood out—the gene was greatly overexpressed in all of the people with pancreatic cancer, but not in any of the others. Sequencing the gene revealed a shared mutation, and further studies on cells growing in culture showed what the abnormal protein does—it alters the cytoskeleton in a way that affects the cells’ ability to form extensions and migrate, movements necessary for invasiveness.

Most mutations that cause cancer are in oncogenes or tumor suppressor genes (Table 18.2). A third category includes mis-

match mutations in DNA repair genes (see section 12.6) that allow other mutations to persist. When such mutations activate oncogenes or inactivate tumor suppressor genes, cancer results. DNA repair disorders are often inherited in a single-gene fashion, and are quite rare. They tend to cause diverse and widespread tumors. An example of a cancer caused by mutation in a mismatch repair gene is hereditary nonpolyposis colorectal cancer (OMIM 120435).

### Oncogenes

Genes that normally trigger cell division when it is appropriate are called **proto-oncogenes**. They are active where and when high rates of cell division are necessary, such as in a wound or in an embryo. When proto-oncogenes are turned on at the wrong time or place, they function as oncogenes (“onco” means cancer).

Abnormal activation of a proto-oncogene into an oncogene may be the result of either

a mutation or a change in expression of the wild type gene. A single base change in a proto-oncogene causes bladder cancer, for example. Alternatively, a proto-oncogene may be moved near a gene that is highly expressed; then it, too, is rapidly or frequently transcribed. For example, a human proto-oncogene is normally activated in cells at the site of a wound, where it stimulates production of growth factors that cause mitosis to fill in the damaged area with new cells. When that proto-oncogene is activated at a site other than a wound—as an oncogene—it still hikes growth factor production and stimulates mitosis. However, because the site of the action is not damaged tissue, the new cells form a tumor.

Some proto-oncogenes encode transcription factors that, as oncogenes, are too highly expressed. (Recall from chapter 10 that transcription factors bind to specific genes and activate transcription.) The products of these activated genes then contribute to the

**Table 18.2**  
Some Cancer Genes

Oncogenes	Cancer Location/Type	Mechanism
<i>myc</i>	Blood, breast, lung, brain, stomach	Alters transcription factor
<i>PDGF</i>	Brain	Alters growth factors or growth factor receptors
<i>RET</i>	Thyroid	Alters growth factors or growth factor receptors
<i>erb-B</i>	Brain, breast	Alters growth factors or growth factor receptors
<i>Her-2/neu</i>	Breast, ovary, salivary glands	Alters growth factors or growth factor receptors
<i>ras</i>	Blood, lung, colon, ovary, pancreas	Affects signal transduction
<i>bcl-2</i>	Blood	Releases brake on apoptosis
<i>PRAD1</i>	Breast, head, and neck	Disrupts cell cycle protein (cyclin)
<i>abl</i>	White blood cells	Translocation alters proto-oncogene and stimulates cell division
<i>uPAR</i>	Breast	Breaks down membranes, easing invasiveness and metastasis
<i>palladin</i>	Pancreas	Disrupts cytoskeleton and enables cancer cell to migrate faster
<b>Tumor Suppressors</b>		
<i>MTS1</i>	Many sites	Releases brake on cell cycle
<i>RB</i>	Eye, bone, breast, lung, bladder	Releases brake on cell cycle
<i>WT1</i>	Kidney	Releases brake on cell cycle
<i>p53</i>	Many sites	Disrupts p53 protein, which normally determines whether DNA is repaired or cell dies
<i>DPC4</i>	Pancreas	Affects signal transduction
<i>NF1</i>	Peripheral nerves	Disrupts inhibition of normal ras, which stimulates cell division
<i>APC</i>	Colon, stomach	Makes nearby DNA more susceptible to replication errors
<i>BRCA1, BRCA2</i>	Breast, ovary, prostate	Faulty repair of double-stranded DNA breaks
<i>hMSH2, hMLH1, hPMS1, hPMS2</i>	Colon, uterus, ovary	Disrupts DNA mismatch repair
<i>Lkb1</i>	Peutz-Jeghers syndrome (many sites)	After birth, fails to block expression of vascular endothelial growth factor, normally active in embryo

cancer cell's characteristics. Oncogenes may also block apoptosis. As a result, damaged cells do not die, but divide.

### Increased Expression in a New Location

A proto-oncogene can be transformed into an oncogene when it is placed next to a gene that boosts its expression. A virus infecting a cell, for example, may insert DNA next to a proto-oncogene. When the viral DNA is rapidly transcribed, the adjacent proto-oncogene (now an oncogene) is also rapidly transcribed. Increased production of the oncogene's encoded protein then switches on genes that promote mitosis, triggering the cascade of changes that leads to cancer. Viruses cause cervical cancer, Kaposi sarcoma, and acute T cell leukemia.

A proto-oncogene can also be activated when it is moved next to a gene that is normally very actively transcribed. This can happen when a chromosome is inverted or translocated, placing a gene in a new chromosomal environment. For example, a cancer of the parathyroid glands in the neck is associated with an inversion on chromosome 11, which places a proto-oncogene next to a DNA sequence that controls transcription of the parathyroid hormone gene. When the gland synthesizes the hormone,

the oncogene is expressed, too. Cells in the gland divide, forming a tumor.

Ironically, the immune system contributes to cancer when a translocation or inversion places a proto-oncogene next to an antibody gene. Recall from chapter 17 that antibody genes normally move into novel combinations when a B cell is stimulated and they are very actively transcribed. Cancers associated with viral infections, such as cervical cancer following HPV infection, may be caused when proto-oncogenes are mistakenly activated with antibody genes. Similarly, in Burkitt lymphoma, a cancer common in Africa, a large tumor develops from lymph glands near the jaw. People with Burkitt lymphoma are infected with the Epstein-Barr virus, which stimulates specific chromosome movements in maturing B cells to assemble antibodies against the virus. A translocation places a proto-oncogene on chromosome 8 next to an antibody gene on chromosome 14. The oncogene is overexpressed, and the cell division rate increases. Tumor cells of Burkitt lymphoma patients have the translocation (**figure 18.12**).

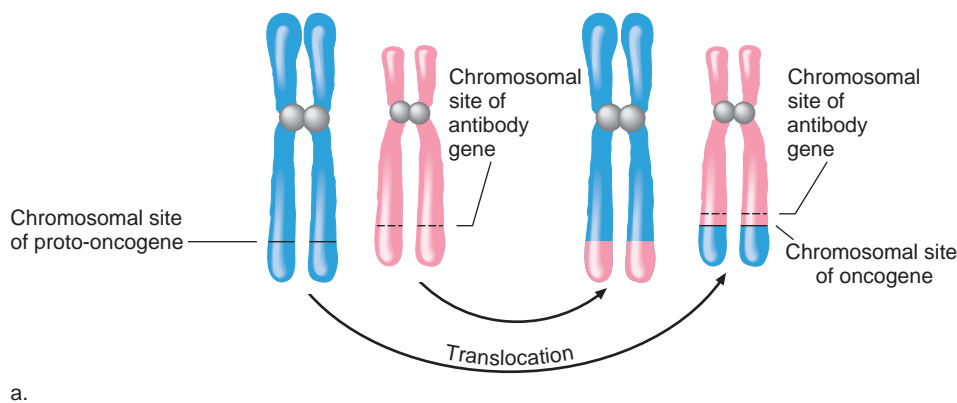
One need not know exactly how changes in gene expression promote cancer to use the information clinically. For example, ocular melanoma affects pigment cells in the eye—it is a much more deadly disease than the more common form of melanoma

in the skin. Many cases spread, and 95 percent of these go to the liver. Researchers extracted mRNAs from affected eyes and measured the expression of 10 genes. From this experiment, they derived two “molecular signatures”—patterns of mRNAs that are more or less abundant than normal—one predicting a low risk of spread to the liver, the other a high risk. This information is used to guide treatment choices.

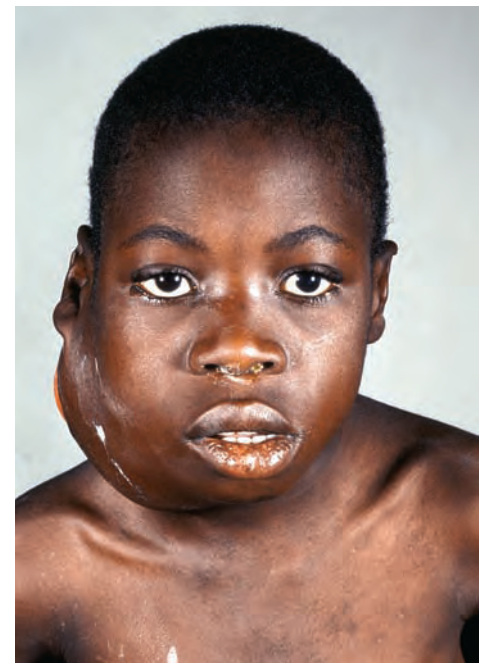
### Fusion Proteins with New Functions

Oncogenes are also activated when a proto-oncogene moves next to another gene, and the gene pair is transcribed and translated together, as if they were one gene. The double gene product, called a **fusion protein**, activates or lifts control of cell division. **Reading 18.1** tells the story of the discovery of the first cancer-causing fusion protein and how it led to the development of an incredibly successful drug.

A fusion oncoprotein causes acute promyelocytic leukemia. (Leukemias differ by the type of white blood cell affected.) A translocation between chromosomes 15 and 17 brings together a gene coding for the retinoic acid cell surface receptor and an oncogene called *myl*. The fusion protein functions as a transcription factor,



**Figure 18.12 A translocation that causes cancer.** (a) The cause of Burkitt lymphoma is translocation of a proto-oncogene on chromosome 8 to chromosome 14, next to a highly expressed antibody gene. Overexpression of the translocated proto-oncogene, now an oncogene, triggers the molecular and cellular changes of cancer. (b) Burkitt lymphoma often affects the jaw.



which when overexpressed causes cancer. The nature of this fusion protein explained an interesting clinical observation—some patients who receive retinoid (vitamin A-based) drugs recover. Their immature, dedifferentiated cancer cells, apparently stuck in an early stage of development where they divide frequently, suddenly differentiate, mature, and then die. Perhaps the cancer-causing fusion protein prevents affected white blood cells from getting enough retinoids to specialize, locking them in an embryoniclike, rapidly dividing state. Supplying extra retinoids allows the cells to continue along their normal developmental pathway.

### Receiving a Too-Strong Division Signal

In about 25 percent of women with breast cancer, affected cells have 1 to 2 million copies of a cell surface protein called Her-2/neu that is the product of an oncogene. The normal number of these proteins is only 20,000 to 100,000.

The Her-2/neu proteins are receptors for epidermal growth factor. The receptors traverse the plasma membrane, extending outside the cell into the extracellular matrix and also dipping into the cytoplasm. They function as a tyrosine kinase, as is the case for CML (see Reading 18.1). When the growth factor binds to the tyrosine of the receptor, the tyrosine picks up a phosphate group, which signals the cell to activate transcription of genes that stimulate cell division. In Her-2/neu breast cancer, too many tyrosine kinase receptors send too many signals to divide.

Her-2/neu breast cancer usually strikes early in adulthood and spreads quickly. However, a monoclonal antibody-based drug called Herceptin binds to the receptors, blocking the signal to divide (see figure 17.20). Interestingly, Herceptin works when the extra receptors arise from multiple copies of the gene, rather than from extra transcription of a single Her-2/neu gene.

### Tumor Suppressors

Some cancers result from loss of a gene that normally suppresses tumor formation by sending growth-inhibiting signals. Block expression of such a gene and the signals stop. Cancer results. Whereas oncogene

activation is usually associated with a point mutation, chromosomal translocation or inversion, and a gain of function, a tumor suppressor gene mutation that causes cancer is usually a deletion that removes a function. One way that viruses cause cancer is by interacting with the normal products of tumor suppressor genes.

Wilms' tumor is a cancer that develops from loss of tumor suppression. When a gene that normally halts mitosis in the rapidly developing kidney tubules in the fetus is absent, a child's kidney retains pockets of cells dividing as frequently as if they were still in the fetus, forming a tumor. Deletion mutations in several genes can cause Wilms' tumor, which is also known as nephroblastoma.

Among the best-studied tumor suppressor genes are the retinoblastoma (RB) gene, the *p53* gene, and *BRCA1*.

### Retinoblastoma (RB)

RB (OMIM 180200) is a rare childhood eye tumor (**figure 18.13**). In 1597, a Dutch anatomist clinically described the eye cancer as a growth "the size of two fists." In 1886, researchers identified inherited cases. At that time, the only treatment was removal of the affected eye. Today, children with an affected parent or sibling, who have a 50 percent chance of having inherited the mutant RB gene, can be monitored from birth so that noninvasive treatment can begin early. Full recovery is common. Often the first abnormal sign is an unusual gray area that appears in an eye in a photograph—the tumor reflects light differently than unaffected parts of the eye.

About half of the 1 in 20,000 infants who develop RB inherit susceptibility to the disorder: They harbor one germline mutant allele for the RB gene in each of their cells. Cancer develops in any somatic cell where the second copy of the RB gene mutates. Therefore, inherited retinoblastoma requires two point mutations or deletions, one germline and one somatic. In sporadic (noninherited) cases, two somatic mutations occur in the RB gene. Either way, RB usually starts in a cone cell of the retina, which provides color vision. Study of RB was the origin of the "two-hit" hypothesis of cancer causation—that two mutations (germline and somatic or two somatic) are required to cause a cancer related to tumor suppressor deletion or malfunction.

Many children with RB have deletions in the same region of the long arm of chromosome 13, which led researchers to the cancer-causing gene. In 1987, they found the RB gene and identified its protein product, which linked the cancer to control of the cell cycle. The protein normally binds transcription factors so that they cannot activate genes that carry out mitosis. It normally halts the cell cycle at G<sub>1</sub>. When the RB gene is mutant or missing, the hold on the transcription factor is released, and cell division ensues.

Mutations in the RB gene cause other cancers. Children successfully treated for retinoblastoma often develop bone cancer as teens or bladder cancer as adults. Mutant RB genes have been found in the cells of patients with breast, lung, or prostate cancers, or acute myeloid leukemia, who never had the eye tumors. These other cancers may be caused by expression of the same genetic defect in different tissues.

### p53 Normally Prevents Many Cancers

Another single gene that causes a variety of cancers when mutant is *p53*. Recall from chapter 12 that the p53 protein transcription factor "decides" whether a cell repairs DNA replication errors or dies by apoptosis. If a cell loses a *p53* gene, or if the gene mutates and malfunctions, a cell with damaged DNA is permitted to divide, and cancer may be the result.



**Figure 8.13 Retinoblastoma.** In inherited retinoblastoma, all of the person's cells are heterozygous for a mutation in the RB gene. A second mutation, occurring in the original wild type allele in cone cells in the retina, releases controls on mitosis. A tumor develops.



## Reading 18.1

### Erin's Story: How Gleevec Treats Leukemia

When 23-year-old *Glamour* magazine editor Erin Zammett Ruddy went for a routine physical in November 2001, she expected reassurance that her healthy lifestyle had indeed been keeping her healthy (**figure 1**). After all, she felt great. What she got, a few days later, was a shock. Instead of having 4,000 to 10,000 white blood cells per milliliter of blood, she had more than 10 times that number—and many of the cells were cancerous.

"I had just returned from a nice, long lunch to find a message from my doctor. Could I call back? Something had come up in my blood work," recalled Erin. "I was diagnosed with chronic myelogenous leukemia. CML is cancer, and until very recently, it proved fatal in the vast majority of cases."

Although there is hardly a "good" time to find out that you have cancer, Erin's diagnosis came just a few months after a landmark report of a new drug—and, ironically, an article in *Glamour* about three CML survivors. A successful cancer drug typically helps about 20 percent of the patients who take it, often just extending life a few months. But cancer in the blood had vanished in 53 of 54 initial patients, usually quickly. So Erin contacted the lead researcher, Brian Druker, and joined the group. Her cancer was reversed—with just a pill a day, and no side effects.

The drug, Gleevec, is now the standard treatment for CML and a few other cancers. The story of its development illustrates how



**Figure 1** "My third bone marrow biopsy—you never get used to the pain," said Erin Zammett-Ruddy. Gleevec has treated her leukemia.

understanding the genetic events that start and propel a cancer can guide development of an effective weapon.

The tale of Gleevec began on August 13, 1958, when two men entered hospitals in Philadelphia and reported weeks of fatigue. Each had very high white blood cell counts and were diagnosed with CML. Too many immature white blood cells were crowding the healthy cells. The men's blood samples eventually fell into the hands of pathologist Peter Nowell and cytogeneticist David Hungerford. They had developed ways to stimulate white blood cells to divide in culture, and they probed the chromosomes of both leukemic and normal-appearing white blood cells in the two tired men and five others with CML.

Nowell and Hungerford discovered a small, unusual chromosome that was only

in the leukemic cells. This was the first chromosome abnormality to be linked to cancer. Later, it would be dubbed "the Philadelphia chromosome" (Ph<sup>1</sup>). The link between the cancer and the chromosome anomaly held up in other patients.

With refinements in chromosome banding, important details emerged. In 1972, Janet Rowley at the University of Chicago used new stains that distinguished AT-rich from GC-rich chromosome regions to tell that Ph<sup>1</sup> is the result of a translocation (see figure 13.20). By 1984, researchers had homed in on the two genes juxtaposed in the translocation between chromosomes 9 and 22. Therein lay the clues that would lead to Erin's treatment.

One gene from chromosome 9 is called the Abelson oncogene (*abl*), and the other gene, from chromosome 22, is called the breakpoint cluster region (*bcr*). Two different fusion genes form. The *bcr-abl* fusion gene is part of the Philadelphia chromosome, and it causes CML. The encoded fusion protein, called the BCR-ABL oncoprotein, is a form of the enzyme tyrosine kinase, which is the normal product of the *abl* gene. The cancer-causing form of tyrosine kinase is active for too long, which sends signals into the cell, stimulating it to divide too many times. (The other fusion gene does not affect health.)

The discovery that a fusion oncoprotein started the cellular changes that cause CML gave drug researchers a target. Through the 1980s, they tested more than 400

More than half of human cancers involve a point mutation or deletion in the *p53* gene. This may be because *p53* protein is a genetic mediator between environmental insults and development of cancer (**figure 18.14**). A type of skin cancer, for example, is caused by a *p53* mutation in skin cells damaged by an excessive inflammatory response that can result from repeated sunburns. That is, *p53* may be the link between sun exposure and skin cancer.

In most *p53*-related cancers, mutations occur only in somatic cells. However, in the germline condition Li-Fraumeni syndrome (OMIM 151623), family members who inherit a mutation in the *p53* gene have a very high risk of developing cancer—50 percent do so by age 30, and 90 percent by age 70. The risk of breast cancer is near 100 percent (see *In Their Own Words* on page 366). A somatic mutation in the affected tissue is necessary for cancer to develop.

#### BRCA 1—A Genetic Counseling Challenge

Breast cancer that runs in families can have two origins: inheritance of a germline mutation followed by a somatic mutation in the same gene in the same cell (familial), or two somatic mutations that happen more than once in a family due to chance (sporadic). Familial breast cancer exhibits many of the complications of Mendel's laws—multiple

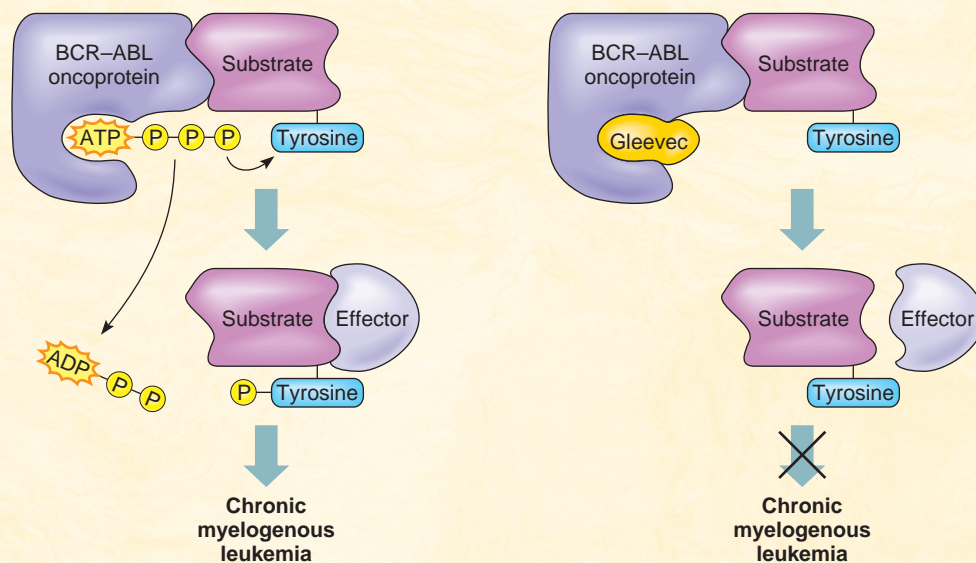


small molecules in search of one that would block the activity of the errant tyrosine kinase, without derailing other important enzymes. When they found a candidate in 1992, Druker joined the effort and led the way in developing it into Gleevec. **Figure 2** shows how the drug works—it nestles into the pocket on the tyrosine kinase that must bind ATP to stimulate cell division. With ATP binding blocked, cancer cells do not receive the message to divide, and they cease doing so. After passing safety tests, the drug worked so dramatically that it set a new speed record for drug approval—10 weeks.

Erin and the other patients were able to track their progress in several ways:

- “Hematological remission” meant that the percentage of leukemia cells in the blood fell.
- “Cytogenetic remission” meant that the percentage of cells with the Ph<sup>1</sup> chromosome fell.
- “Molecular remission” meant that the level of mRNA representing the fusion gene fell.

Although molecular remission is the goal of CML treatment, in actuality, fusion gene mRNA rarely reaches undetectable levels. As a result, patients can become resistant to Gleevec—relapse occurs in 3 to 16 percent of patients, depending on how sick they were when diagnosed. Resistance is a result of natural selection. Those few cancer cells able to divide in the presence of the



**Figure 2** How Gleevec treats chronic myelogenous leukemia. In CML, a translocation forms the fusion oncoprotein BCR-ABL, which functions as a tyrosine kinase. A tyrosine on a substrate molecule picks up a phosphate from the ATP nestled in the oncoprotein, making the substrate able to bind to another protein, called an effector, that triggers runaway cell division (**a**). Gleevec replaces the ATP (**b**). Without phosphorylation of the tyrosine on the substrate, division of the abnormal cells stops. As cancer progresses, some cells undergo mutations that make the shape of their pockets unable to bind the drug. Newer drugs can replace Gleevec once the cancer becomes resistant.

Source: Adapted from “Drug therapy: Imatinib mesylate—A new oral targeted therapy” by Savage & Antman; *New England Journal of Medicine* 346: 683–693. Copyright © 2002 Massachusetts Medical Society. All rights reserved. Reprinted by permission.

drug eventually take over. Again, genetic research came to the rescue. By discovering how resistant cells evade the drug, researchers tweaked Gleevec, making it bind more strongly, and developed new drugs that fit the slightly altered active site in resistant cancer cells.

As for Erin, after talking to other young women with CML, she decided to go off the drug while pregnant. Although she risked relapse, she did not want to expose a fetus to the powerful drug. Follow her progress on her blog: <http://www.glamour.com/life-style/blogs/editor>.

alleles, incomplete penetrance, variable expressivity, environmental influences, genetic heterogeneity, and polygenic inheritance and epistasis. It also illustrates sex-limited inheritance, for males can transmit the mutation even though they are rarely affected.

Because breast cancer is so common, some women seeking genetic counseling may have sporadic cases that appear to be inherited—or the reverse. **Table 18.3** highlights some of the challenges encountered in genetic counseling for breast cancer.

Only 5 percent of breast cancers are familial, and of these, 15 to 20 percent are caused by mutations in the genes *BRCA1* or *BRCA2*. The *BRCA1* gene, which stands for “breast cancer predisposition gene 1,” greatly increases the lifetime risk of inheriting breast and ovarian cancer. It is a tumor suppressor gene, because the phenotype results from a loss of function. In the most common mutation, two adjacent bases are deleted, altering the reading frame and shortening the protein. The mutation is

inherited as an autosomal dominant trait, but with late onset of symptoms and incomplete penetrance.

*BRCA1* encodes a large protein that is normally in the nucleus, where it activates transcription of the genes that respond to p53 protein. Therefore, *BRCA1* protein is necessary for DNA repair—specifically, mending double-stranded breaks that could threaten the stability of chromosomes.

*BRCA1* mutations have different incidences in different populations, and the risk



### p53: A Family's View

Of the 35 distinct cancer syndromes, Li-Fraumeni is one of the rarest. A germline mutation sets the stage for multiple, early cancers. Patricia Holm's family is one of only about 100 known to have the condition. Here is her story:

At 25 years old, Timothy Whittaker, my husband, developed liposarcoma, a rare cancer of the fat cells. He suffered greatly and weighed at the time of his death 55 pounds—eight months after diagnosis.

The younger of our girls, Jennifer Leigh, was born in 1973. She was perfectly healthy throughout her childhood, but as her school career began, she had trouble in her studies. I have since wondered if the tumor was growing even then. The summer between her junior and senior years, when she was 17, Jennifer developed a headache that sent us three times in four days to the E.R. On the fourth day, a CT scan revealed a lemon-sized tumor in her left parietal lobe. The first resection pathology revealed a pleomorphic xanthoastrocytoma. Four months later, pathology revealed anaplastic astrocytoma. After nine months of chemotherapy and radiation, the tumor was back, the pathology report indicating glioblastoma multiforme—a death sentence. In the 27 months from diagnosis to death, every approved and unapproved method of treatment was used, and nothing ever helped . . . we went to four states and two countries seeking a cure. There wasn't one, and exactly 19 years after the death of Timothy, Jennifer died at the age of 20.

Doctors assured me that liposarcoma and brain tumors have absolutely no connection. Bad luck? A witch's curse? What was going on? The answer would come much later.

In August 1998 our daughter, Kimberly, gave birth to a baby girl, Grace. Shortly thereafter she felt a thickening in her left breast. Repeated attempts to alert her ob/gyn failed, as he saw this as a normal breast change, probably a clogged milk duct. In May 2000, Kim felt a lump under her arm that in three weeks became the size of a golf ball. She then had her general medical doctor take a look and he sent her for a mammogram the same day. A lump was not seen on the mammogram, but her breast was full of microcalcifications and looked like a starry night! An ultrasound was done, and there on the screen was an enormous black mass. Oh my God, not again.

The next year and a half consisted of chemotherapy, radiation, double mastectomies and 40 weekly treatments of Herceptin. Pathology was intraductal carcinoma. After all her treatments, the pathology on the removed breasts was ductal carcinoma *in situ* only; she had a complete response to chemotherapy. Finally, a victory over cancer! Today Kim is doing very well.

Shortly after diagnosis, a genetic work-up revealed that Kim had Li-Fraumeni syndrome. Grace, who has a 50/50 chance of having inherited the mutation, has not been



**Figure 1** Grace has not been tested for Li-Fraumeni syndrome.

tested (**figure 1**). But as you can imagine, for both Grace and her mother there is no such thing as a simple headache, no harmless sore throat, no lymph node that loving fingers don't glide over in hopes that there will be no knot under the skin. It can be a daily struggle to live with the knowledge that there is a bomb ticking in every cell of your body that is lying in wait for the right stimulus to set it off.

Patricia Holm

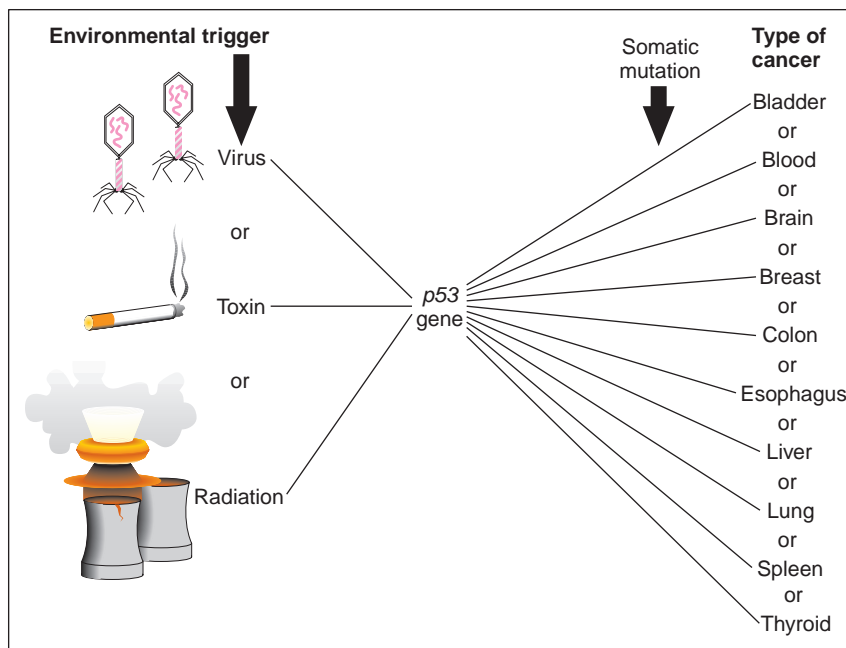
of cancer varies in different populations, indicating that the *BRCA1* protein interacts with other proteins and perhaps with environmental factors, too (**table 18.4**). Only 1 in 833 people in the general U.S. population has a mutant *BRCA1* allele. In one large study of women with breast cancer, 2.9 percent of the white women had *BRCA1* mutations, compared to 1.4 percent of the black women. But among the Ashkenazic Jewish population, slightly more than 2 percent of all individuals have one mutant *BRCA1* allele. It was in such families that

the *BRCA1* gene was discovered—several members became ill at very young ages. In this group, a woman who inherits a *BRCA1* mutation faces a greater than 80 percent risk of developing breast cancer over her lifetime and a 50 percent risk of developing ovarian cancer. Some still-healthy relatives with the mutant gene have had the affected organs removed to prevent the cancers. But risk, even if a *BRCA1* or *BRCA2* mutation is inherited, is difficult to predict because of environmental factors. Women with such a mutation born after 1940 have a higher risk

than those born earlier, suggesting a nongenetic influence.

*BRCA2* breast cancer is also more common among the Ashkenazim. This gene encodes a nuclear protein that is even larger than the *BRCA1* protein. Ashkenazic women who inherit a mutation in *BRCA2* face a 60 to 85 percent lifetime risk of developing breast cancer and a 10 to 20 percent risk of developing ovarian cancer. Men who inherit a *BRCA2* mutation have a 6 percent lifetime risk of developing breast cancer, which is 100 times the risk for men in the





**Figure 18.14** *p53* cancers reflect environmental insults. The environment triggers mutations or changes in gene expression that lead to cancer. The *p53* gene may be a mediator—it has been called “the guardian of the genome.”

**Table 18.3**

### The Complexities of Providing Genetic Counseling for Familial Breast Cancer

1. Many mutations and polymorphisms are known in breast cancer genes.
2. When more than one case occurs in a family, it can be either familial or sporadic. A woman who does not have a *BRCA1* or *BRCA2* mutation can still develop breast cancer. A woman with no affected relatives can have a *BRCA1* or *BRCA2* mutation.
3. *BRCA1* and *BRCA2* are incompletely penetrant—that is, inheriting a disease-causing allele does not always mean developing cancer.
4. The risk associated with *BRCA1* or *BRCA2* mutations varies depending upon interactions with other genes as well as environmental exposures.

general population. In the study just mentioned, 2.1 percent of the white women had *BRCA2* mutations, compared to 2.6 percent of the black women. Inheriting a *BRCA2* mutation also increases the risk of developing cancers of the colon, kidney, prostate, pancreas, gallbladder, skin or stomach.

**Table 18.4**

### Lifetime Risk That Inheriting a *BRCA1* Mutation Will Lead to Breast Cancer

Group	Risk (%)
Ashkenazim with confirmed strong family history of early-onset cases	87
Ashkenazim with family history of breast cancer, but not early onset or many affected members	56
Ashkenazim with no family history of breast cancer	36
General population	8–10

The fact that *p53*, *BRCA1*, and *BRCA2* proteins all bind to each other in the nucleus suggests that they interact to enable a cell to repair double-stranded DNA breaks. *BRCA2* also pulls apart daughter cells as mitosis completes. Mutations in this gene may explain the aneuploidy (extra or missing chromosomes) that is common in cancer cells.

Still other genes that affect these three (*BRCA1*, *BRCA2*, and *p53*) can cause breast cancer. For example, the product of a gene called *ATM* adds a phosphate to the product of a gene called *CHEK2*, which then adds a phosphate to the *BRCA1* protein. Mutations in *ATM* and *CHEK2* also cause breast cancer. Another form of breast cancer results from mutations in any of five genes known to cause Fanconi anemia, a fatal blood disorder. Five of the Fanconi anemia proteins form a cluster that activates a sixth protein, which in turn binds to and inactivates the *BRCA2* protein.

The many ways to develop breast cancer indicate that this isn’t one illness, but probably ten to twenty different types. In each type, disruptions of a signal transduction pathway or DNA repair mechanism accelerate the cell cycle in the affected tissue, which is usually a milk duct.

## Key Concepts

1. Proto-oncogenes normally control the cell cycle. They can become oncogenes when they mutate, move next to a gene that is highly expressed, or are transcribed and translated with another gene, forming a fusion protein.
2. Mutations in tumor suppressor genes usually are deletions that cause a cell to ignore extracellular constraints on cell division.

## 18.5 A Series of Genetic Changes Causes Some Cancers

Most cancers reflect the interplay of several genes. Certain single genes, when mutant, can have a generalized effect, causing a chromosomal instability that sets the stage for cancer. This is the case for a gene called *BUB1B*. Mutations in this gene cause mosaic variegated aneuploidy (OMIM 257300), in which about a quarter of a person’s cells have missing or extra chromosomes. The autosomal recessive condition causes various types of childhood cancer. The functional gene ensures that the correct number of chromosomes is distributed to daughter cells as mitosis completes.

Genes that guide a cell toward the cancerous state when mutant are sometimes considered in two broad categories, based on their effects. “Gatekeeper” genes control mitosis and apoptosis, which must be in balance to maintain the number of cells forming the affected tissue. Their effect is direct. “Caretaker” genes, in contrast, control the mutation rates of gatekeepers, and may have the overall effect, when mutant, of destabilizing the genome.

Some cancers are the culmination of a series of changes in several specific genes, involving gatekeepers and caretakers. To identify the steps, researchers examine tumor cell DNA from people in various stages of the same type of cancer. The older the tumor, the more genetic changes accumulate. Therefore, a mutation present in all stages acts early in the disease process, whereas a mutation seen only in the tumor cells of sicker people functions late in the process. Each step provides a potential point of treatment. Following is a closer look at two types of cancer that reflect a series of genetic changes.

## A Rapidly Growing Brain Tumor

Astrocytomas, the most common types of brain tumors, affect cells called astrocytes. These tumors grow quickly. The man whose brain is shown in **figure 18.15** died just three months after noticing twitching in an eye. During that time, a series of single-gene and chromosomal changes occurred. Loss

of both *p53* alleles came early because this change appears in many early-stage tumor cells, as well as in later ones.

By the time an astrocytoma has grown into a small tumor, another genetic change is apparent—loss of both alleles of several genes on chromosome 9. Some of the missing genes encode interferons, so the loss probably disrupts immune protection against the developing cancer. Two other deleted genes encode tumor suppressors.

At least two additional mutations speed the tumor’s growth. First, an oncogene on chromosome 7 is activated, overexpressing a gene that encodes a cell surface receptor for a growth factor. The cancer cells bear too many growth factor receptors and receive too many messages to divide. Finally, the cancer cells lose one or even both copies of chromosome 10. This is a final change, because it is seen in all end-stage tumors, but not in early ones.

## Colon Cancer

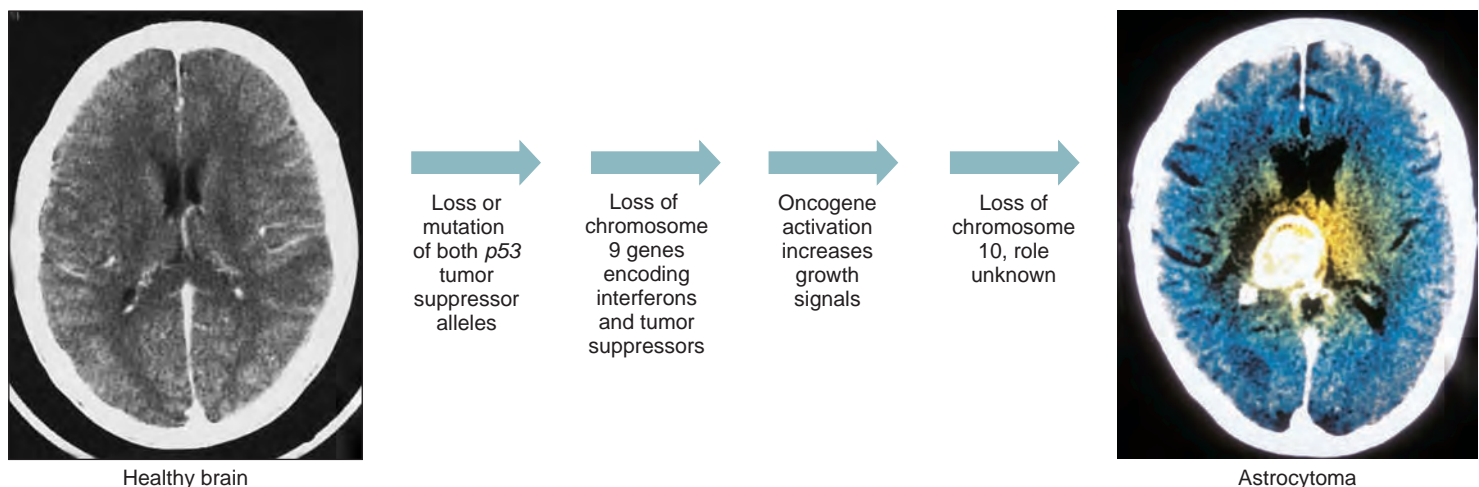
Colon (large intestine) cancer does not usually occur in families with the frequency or pattern expected of a single-gene disorder. However, when family members with non-cancerous growths (polyps) in the colon are considered with those who have colon cancer, a Mendelian pattern emerges. Five percent of colon cancer cases are inherited. One in 5,000 people in the United States has precancerous colon polyps, a condition called familial adenomatous polyposis (FAP; OMIM 175100).

FAP begins in early childhood with tiny colon polyps, often hundreds, that progress over many years to colon cancer. Colon lining cells typically live three days. In FAP, they fail to die on schedule and instead build up, forming polyps. Connecting FAP to the development of colon cancer enabled researchers to view the stepwise progression of a cancer (**figure 18.16**). Both oncogenes and tumor suppressors take part.

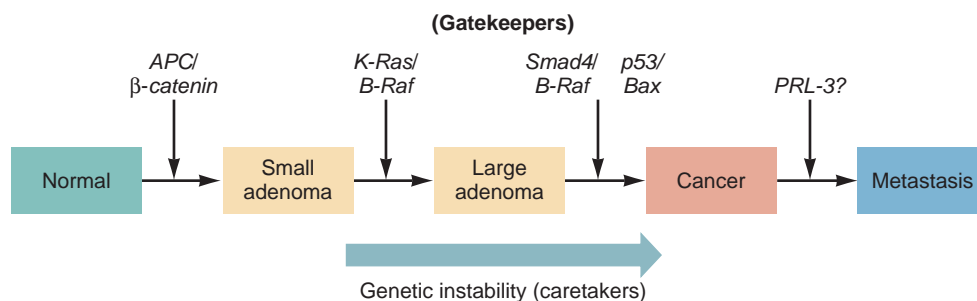
The study of the hereditary nature of some colon cancers began at the University of Utah in Salt Lake City in the fall of 1947, when young professor Eldon Gardner stated that he thought cancer might be inherited. A student, Eugene Robertson, excitedly told the class that he knew of a family in which a grandmother, her three children, and three grandchildren had colon cancer.

Intrigued, Gardner delved into the family’s records and began interviewing relatives. He eventually found 51 family members and arranged for each to be examined with a colonoscope, a lit instrument passed into the rectum to view the wall of the colon. The colons of 6 of the 51 people were riddled with the gobletlike precancerous polyps, although none of the 6 had symptoms. Removal of the affected tissue probably saved their lives.

In the years that followed, researchers identified other families with more than one case of colon polyps. Individuals with only polyps were diagnosed with FAP. If a person with colon polyps had cancer elsewhere, extra teeth, and pigment patches in the eye, the condition was called Gardner syndrome,



**Figure 18.15** Several genes can contribute to a cancer. A series of genetic changes transforms normal astrocytes, which support nerve cells in the brain, into a rapidly growing cancer.



**Figure 18.16 Several mutations contribute to FAP colon cancer.** Cells lining the colon divide more frequently when the *APC* gene on chromosome 5q undergoes a point mutation, causing small benign tumors (adenomas) to form. Activation of certain oncogenes, such as *K-Ras* and *B-Raf*, fuel growth of the adenomas. Mutations in *p53* and other genes push the adenoma cells to become cancerous. Finally, mutations in a gene called *PRL-3* trigger metastasis. Caretaker genes cause genetic instability that contributes to the disease process.

named for the professor. Researchers identified the chromosomal defect that causes Gardner syndrome in 1985 with the help of a 42-year-old man at the Roswell Park Cancer Institute in Buffalo, New York. He had several problems—no gallbladder, an incomplete liver, an abnormal kidney, mental retardation, and Gardner syndrome. To a geneticist, a seemingly unrelated combination of symptoms suggests a chromosomal abnormality affecting several genes. Sure enough, the man's karyotype revealed a small deletion in the long arm of chromosome 5. This was the first piece to the puzzle of colon cancer. Today, intestinal cells in stool samples can be tested for absence of a protein called APC, indicating the first step in this route to colon cancer.

The deletion in chromosome 5 detected in the man from Buffalo in 1985 removed the *APC* gene. This is the main “gatekeeper” for this type of colon cancer, and is the first step depicted in figure 18.16. Normally APC protein binds to another protein, b-catenin, causing a phosphate to be added to it. The phosphorylation prevents b-catenin from acting. But when the *APC* gene is deleted, b-catenin isn't silenced, and instead it enters the nucleus and activates genes that promote mitosis. The cell becomes unable to stop dividing. A tumor forms, but it is not yet malignant. Other pathways, such as those controlled by the genes *TGF* and *p53*, push the abnormal cells to become cancerous. *TGF* normally inhibits mitosis, and *p53* normally sends cells to a fate of apoptosis. *PRL-3* is a gene that acts late in the process, enabling the cancer to spread. Several caretaker genes affect the expression of the gatekeepers, so the overall picture is quite complex.

## Key Concepts

1. A single mutant gene can destabilize chromosomes, causing aneuploidy that precedes cancer.
2. Some cancers may be the culmination of a series of mutations in several genes.
3. Determining which mutations are present in particular stages of a cancer can reveal the sequence of gene actions.

## 18.6 Environmental Causes of Cancer

Environmental factors contribute to cancer by mutating or altering the expression of genes that control the cell cycle, including apoptosis and DNA damage control (repair). Inheriting a susceptibility gene places a person farther along a particular road to cancer, but cancer can happen in somatic cells in anyone. Since we cannot do much about our genes, it makes sense to identify environmental cancer triggers and develop ways to control them or limit our exposure to them.

Looking at cancer at a population level reveals the interactions of genes and the environment. For example, researchers examined samples of non-Hodgkin lymphoma tumors for a specific translocation associated with the tumor. The samples were from farmers and had been stored for several years. Of the 172 samples, 65 had the translocation. The individuals who had the translocation were much more likely to have been exposed for long times to

toxic insecticides, herbicides, fungicides, and fumigants, compared to the other patients. Therefore, the exposures correlate to the translocation-associated form of the lymphoma.

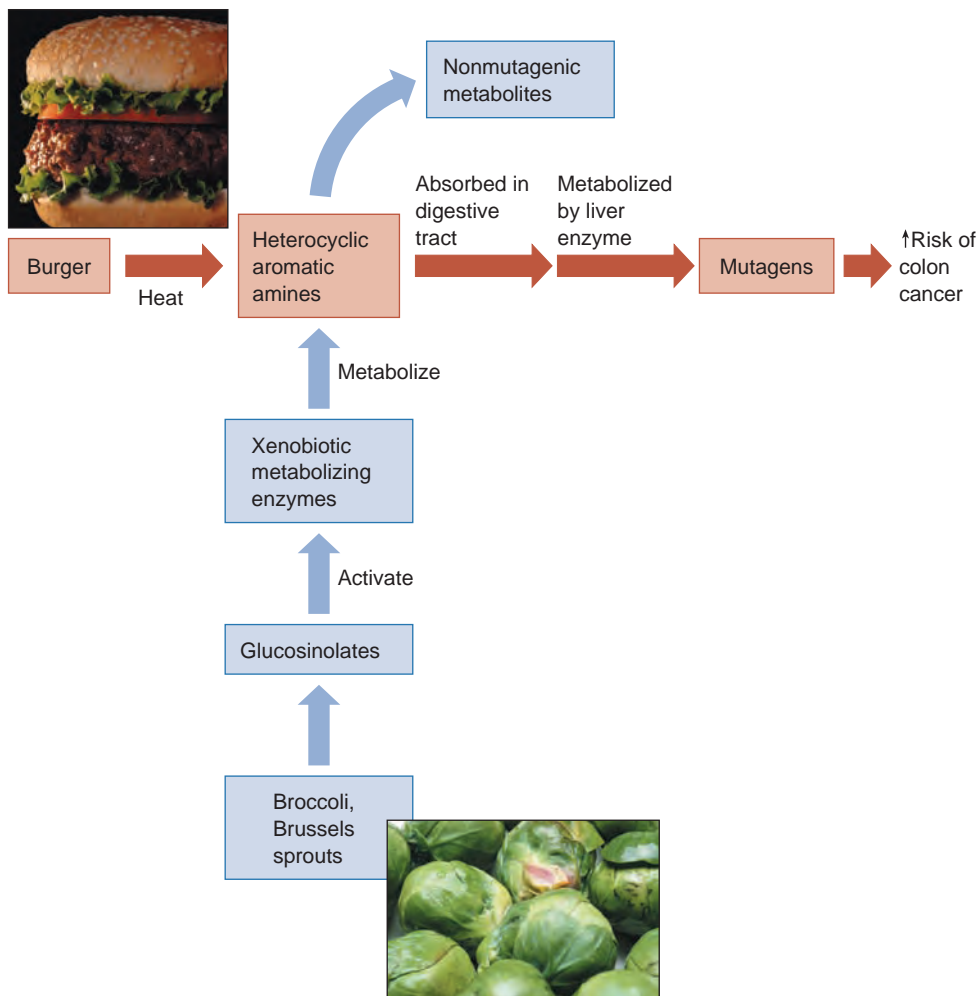
On an individual level, one way to lower the chance of developing cancer is to avoid certain high-risk environmental factors, such as cigarette smoking and excess sun exposure. A more active approach to minimize environmental influences on cancer risk is chemoprevention, which is taking certain nutrients, plant extracts, or drugs. Promising “chemopreventatives” include folic acid, vitamins D and E, selenium, compounds from soybean, tomato, and green tea, and certain anti-inflammatory drugs.

## Considering Carcinogens

Determining precisely how an environmental factor such as diet affects cancer risk can be complicated. Consider the cruciferous vegetables, such as broccoli and brussels sprouts, which are associated with decreased risk of developing colon cancer. These vegetables release compounds called glucosinolates, which in turn activate “xenobiotic metabolizing enzymes” that detoxify carcinogenic products of cooked meat called heterocyclic aromatic amines. With a vegetable-poor, meaty diet, these amines accumulate. They cross the lining of the digestive tract and circulate to the liver, where enzymes metabolize them into compounds that cause the mutations associated with colon cancer (figure 18.17).

Exposure to carcinogens—in the workplace, home, or outdoors—can raise cancer risk. Chemical carcinogens were recognized as long ago as 1775, when British physician Sir Percival Potts suggested that the high rate of skin cancer in the scrotums of chimney sweeps in London was due to their exposure to a chemical in soot. Since then, epidemiological studies have identified many chemicals as possibly causing cancer in certain populations (Table 18.5). However, most studies reveal correlations rather than cause-and-effect relationships. In the strongest cases, genetic or biochemical evidence explains the observed environmental connection.





**Figure 18.17 One way that cruciferous vegetables lower cancer risk.** Compounds called heterocyclic aromatic amines form in cooking meat, are absorbed into the digestive tract, and are metabolized by a liver enzyme into mutagens, which may cause colon cancer. Broccoli and brussels sprouts produce glucosinolates, which activate xenobiotic metabolizing enzymes that block part of the pathway that leads to production of the mutagens.

## Methods to Study Cancer-Environment Links

Epidemiologists use different statistical tools to link environmental exposures and cancer. Connections are strengthened when different types of investigations yield consistent results. This is true, for example, of the association between eating whole grain cereals and reduced incidence of colorectal cancer.

Epidemiological studies of cancer causation compare people in different ways. A **population study** compares the incidence of a type of cancer among very different groups of people. If the incidence differs, then some distinction among the populations may be responsible. For example, an oft-mentioned study from 1922 found that primitive societies have much lower rates of many cancers than more developed societies. The study attributed the lack of cancer to the high level of physical activity among the primitive peoples—but diet might also have explained the difference.

Population studies often have too many variables to clearly establish cause and effect. Consider the very high incidence of breast cancer on Long Island, New York. One hypothesis attributes the mini-epidemic to pesticide exposure, but this population also has a high frequency of *BRCA1* mutations among its Ashkenazi citizens. Sociological factors come into play, too. In this population, women have frequent mammograms starting at a young age. As a result, the percentage of the population with recognized early stages of the disease may be higher than in other populations where women are less likely to have regular mammograms. All

**Table 18.5**

**Increase in Death Rates for Certain Cancers in Certain Areas in the United States**

Cancer Type	Region	Possible Explanation
Breast	Northeast	<i>BRCA1</i> mutations, greater lifetime exposure to estrogens (early menstruation, late menopause, older age of first birth, exposure to pesticides)
Colon	Northeast	Dietary factors, diagnostic radiation exposure
Lung	White men in south, white women in west, blacks in northern cities	Changes in regional trends in cigarette smoking
Lung	Men in southern coastal areas	Asbestos exposure while working in shipyards during World War II
Mouth, throat	Women in rural south	Smokeless tobacco
Esophagus	Washington, D.C., coastal South Carolina	Alcohol and tobacco, dietary deficiencies of fruits and vegetables

of these factors may contribute to the high breast cancer incidence in this area.

More informative than a population study is a **case-control study**, in which people with a type of cancer are matched with healthy individuals for age, sex, and other characteristics. Then researchers look for differences between the pairs. If, for example, the cancer patients had extensive dental X rays at a young age but the control group didn't, X-ray exposure may be a causal factor. Limitations of this type of study are that much of the information is based on recall, people make mistakes, and not all relevant factors are identified and taken into account.

The most informative type of epidemiological investigation is a **prospective study**. Two or more groups of people follow a specified activity plan, such as a dietary regimen, and are checked periodically for cancer. By looking ahead, the investigator has more control over the activities and can verify information. However, a limitation of this type of cancer study is that cancer usually takes many years to appear and progress.

Once epidemiological studies indicate a correlation, a biological explanation is necessary to draw conclusions or even suggest further studies. For example, finding lower cancer rates among vegetarians might be explained by the observation that certain vegetables contain antioxidant compounds, which deactivate the free radicals that can damage DNA, thereby preventing mutations.

### 18.7 Evolving Cancer Diagnosis and Treatment

Estimating the risk that a certain type of cancer will occur in a particular individual is only possible for a few disorders that are inherited in a single-gene fashion through known genes. More often, discovery of cancer follows a screening test such as mammography or high levels of prostate specific antigen in the bloodstream, or after symptoms occur or a person feels a lump. Then treatments begin—and there are usually many options.

The oldest cancer treatment is surgery—it prevents invasiveness by removing the tumor. Some people have surgery to remove organs that have a high probability of

becoming cancerous, based on the results of genetic tests. This is most commonly done to prevent breast or ovarian cancer, after tests indicate a mutation in the *BRCA1* or *BRCA2* genes. Two other common treatment approaches are radiation and chemotherapy, which kill all cells that divide rapidly. This also affects healthy cells in the digestive tract, hair follicles, and bone marrow, causing side effects of nausea, hair loss, great fatigue, and susceptibility to infection. Patients receive several other drugs to help them tolerate the side effects, including colony stimulating factors to replenish bone marrow. These other drugs enable patients to withstand higher and more effective doses of chemotherapy.

Several newer types of cancer drugs affect cancer cell characteristics or activities other than hiked division rate. Some treatments:

- stimulate cells to regain specialized characteristics, such as drugs based on retinoic acid.
- inhibit telomerase, which prevents cancer cells from elongating their telomeres and continually dividing.
- induce apoptosis, which halts cell division.
- Inhibit angiogenesis, which robs a cancer of its blood supply.

The development of angiogenesis inhibitors is particularly interesting, because it illustrates the difficulty of pursuing an unusual idea. The term *angiogenesis* was coined by a British surgeon in 1787 to describe the growth of blood vessels in a reindeer's antler. It was described in detail in 1935 in the placenta of a pregnant

monkey. In 1971, another surgeon, Judah Folkman of Harvard University, suggested that angiogenesis is required to nourish a cancerous tumor, and he pursued research on blocking the process. His work was largely unknown to the public until 1998, when a prominent newspaper hyped an off-the-cuff comment that DNA-discoverer James Watson made to a reporter, claiming that Folkman would “cure cancer in two years.” He didn't. However, today more than fifty drugs that starve a tumor of its blood supply are being tested. The first anti-angiogenesis drug, Avastin, was approved in 2004 to treat colorectal cancer, in combination with chemotherapy. Anti-angiogenesis drugs have several effects: they stop the blood supply to the tumor, they make the tumor soak up more chemotherapy drugs, they kill tumor cells directly, and they stimulate the immune response.

Diagnostic tests and treatments for cancer have become more targeted and more rational, zeroing in on cancer cells while sparing healthy ones. The approach to breast cancer illustrates how genetic and genomic information is refining management of these diseases (**table 18.6**). The first targeting came with recognition that breast cancer cells have receptors for two hormones, estrogen or progesterone. Women with estrogen receptor-positive tumors begin a several-year course of a drug that blocks these receptors from receiving signals to divide or a drug that inhibits an enzyme called aromatase, required to produce estrogen.

Determining estrogen receptor status is subtyping by phenotype. With the discovery of single genes that cause cancer, diagnosis

Table 18.6 Evolution of Treatments for Breast Cancer	
Strategy	Examples
Remove or destroy cancerous tissue Use phenotype to select drug	Surgery, radiation, chemotherapy Estrogen receptor-positive women take a selective estrogen receptor modulator or an aromatase inhibitor or both
Use genotype to select drug	Women with <i>Her-2/neu</i> -positive cancers take Herceptin (monoclonal antibody)
Genomic level	Gene expression profile on DNA microarray used to guide drug choice; 70-gene signature predicts metastasis

began to include genotyping; a woman might have *BRCA1* or *Her-2/neu* breast cancer.

Increasingly, cancer diagnosis utilizes DNA microarrays that scan both genotype for cancer-associated mutations and as well as gene expression patterns, enabling physicians to match a particular patient to the treatments most likely to work right from the start, or predict metastasis. For example, a test that evaluates the expression of seventy genes is used to identify early-stage breast cancers that are most likely to recur after treatment. Mutation and gene expression analyses can also identify patients likely to suffer side effects from particular drugs. Gene expression profiles are sometimes called signatures.

The limitation of any cancer treatment, old or new, is defined by the strength of the enemy. Cancer cells are incredibly abundant and ever-changing. Surgery followed by a barrage of drugs and radiation can slow the course of the disease, but all it takes is a few escaped cancer cells—called

micrometastases—to sow the seeds of a future tumor. The DNA of cancer cells mutates in ways that enable the cells to pump out any drug sent into them. In addition, cancer cells have redundancies, so that if a drug shuts down angiogenesis or invasiveness, the cell completes the task another way. Although cancer treatments can cure, it is more likely that they kill enough cancer cells, and sufficiently slow the spread, so that it takes the remainder of a lifetime for the tumors to grow back. In this way, cancer becomes a chronic, manageable condition.

Even as targeted cancer treatments are becoming available, continuing analysis of the human genome is revealing that our view of cancer as a derangement of the cell cycle may be a great oversimplification. A preliminary scan of breast and colon tumors detected 189 genes that mutate as the disease progresses—the screen identified well-known cancer genes such as those discussed in this chapter, but the majority

had never been implicated in cancer before, such as genes that control cell adhesion. In addition, the same type of cancer in different individuals often had different mutations. The overall conclusion: we still have a lot to learn about cancer.

## Key Concepts

1. Lower cancer risk is associated with eating more fruits, vegetables, and whole grain.
2. Treatments for cancer target the characteristics of cancer cells. Surgery removes tumors. Chemotherapy and radiation nonselectively destroy rapidly dividing cells.
3. Newer treatments target receptors on cancer cells, block telomerase, stimulate differentiation, or attack a tumor's blood supply.
4. Diagnosis and treatment of cancer will increasingly consider genomic information.

## Summary

### 18.1 Cancer Is Genetic, But Usually Not Inherited

1. Cancer is a genetically dictated loss of cell cycle control, creating a population of highly proliferative cells that outgrows and overwhelms surrounding tissue.
2. Sporadic cancers result from **somatic mutations**. They are more common than cancers that are caused by **germline mutations** plus somatic mutations in affected tissue. Cancer may be polygenic. Changing gene expression patterns also contribute to cancer, and can be used to distinguish types.
3. Mutations in genes that encode or control transcription factors, cell cycle checkpoint proteins, growth factors, repair proteins, or telomerase may disrupt the cell cycle, causing cancer.

### 18.2 Characteristics of Cancer Cells

4. A tumor cell divides more frequently or more times than cells surrounding it, has altered surface properties, loses the specializations of the cell type it arose

from, and produces daughter cells like itself.

5. A malignant tumor infiltrates tissues and can **metastasize** by attaching to basement membranes and secreting enzymes that penetrate tissues and open a route to the bloodstream. From there, a cancer cell can travel, establishing secondary tumors.

### 18.3 Origins of Cancer Cells

6. Cell specialization and position within a tissue are important determinants of whether cancer begins.
7. **Cancer stem cells** can divide to yield cancer cells and abnormally differentiated cells.
8. A cell that dedifferentiates and/or turns on expression of “stemness” genes can begin a cancer.
9. A mutation that enables a cell to divide continually can alter the percentages of cells in a tissue that can divide, resulting in an abnormal growth.
10. Chronic repair of tissue damage can provoke stem cells into producing an abnormal growth.

### 18.4 Cancer Genes

11. Cancer is often the result of activation of **proto-oncogenes** to **oncogenes**, and inactivation of **tumor suppressor** genes. Mutations in DNA repair genes cause cancer by increasing the mutation rate.
12. Proto-oncogenes normally promote controlled cell growth, but are overexpressed because of a point mutation, placement next to a highly expressed gene, or transcription and translation with another gene, producing a **fusion protein**. Oncogenes may also be overexpressed growth factor receptors.
13. A tumor suppressor is a gene that normally enables a cell to respond to factors that limit its division.

### 18.5 A Series of Genetic Changes Causes Some Cancers

14. Many cancers result from two hits or mutations, but some entail a longer series of genetic changes.
15. To decipher the gene action sequences that result in cancer, researchers examine the mutations in cells from patients at various



stages of the same type of cancer. Those mutations present at all stages of the cancer are the first to occur.

16. Astrocytoma and FAP are two cancers that require several mutations to develop.

### 18.6 Environmental Causes of Cancer

17. **Population, case-control, and prospective studies** can correlate

environmental exposures to development of certain cancers. Biochemical and/or genetic evidence can sometimes explain epidemiological observations.

### 18.7 Evolving Cancer Diagnosis and Treatment

18. Traditional cancer treatments are surgery, radiation, and chemotherapy.

Newer approaches block hormone receptors, stimulate cell specialization, block telomerase, and inhibit angiogenesis. A genomic approach identifies mutations and differences in gene expression that define cancer subtypes.

## Review Questions

1. Cite three ways that cancer involves abnormal gene function.
2. Explain how changes in gene expression differ from germline mutations in oncogenes or tumor suppressor genes in terms of transmitting cancer susceptibility to offspring.
3. Why don't all cancers of the same cell type respond to the same drug?
4. How is the cell cycle controlled from outside and inside the cell?
5. What is inaccurate about the statement that "cancer cells are the fastest dividing cells in the body?"
6. Is any cell with long telomeres a cancer cell?
7. What would be the value of knowing whether a person's cancer is sporadic or inherited?
8. List four characteristics of cancer cells.
9. Describe four ways that cancer might originate at the cell or tissue level.
10. How can the same cancer be associated with deletions as well as translocations of genetic material?
11. Three percent of all cancer cells have chromosome rearrangements. What other type of genetic change might be present in a cancer cell?
12. Distinguish among the following types of studies:
  - a. population
  - b. case-control
  - c. prospective
13. List four new strategies for treating cancer, and explain how they work.

## Applied Questions

1. An individual can develop breast cancer by inheriting a germline mutation, then undergoing a second mutation in a breast cell; or by undergoing two mutations in a breast cell, one in each copy of a tumor suppressor gene. Cite another type of cancer, discussed in the chapter, that can arise in these two ways.
2. How do the mechanisms of the drugs Gleevec and Avastin differ?
3. A young black woman thinks that she cannot get a *BRCA* form of breast cancer because she isn't Jewish. Is she correct?
4. von Hippel-Lindau syndrome (OMIM 193300) is an inherited cancer syndrome. The responsible mutation lifts control over the transcription of certain genes, which, when overexpressed, cause tumors to form in the kidneys, adrenal glands, and blood vessels. Is the von Hippel-Lindau gene an oncogene or a tumor suppressor? Cite a reason for your answer.
5. The *BRCA2* gene causes some cases of Wilms' tumor and some cases of breast cancer. Explain how the same tumor suppressor mutation can cause different cancers.
6. Ads for the cervical cancer vaccine present the fact that a virus can cause cancer as startling news, when in fact this has been known for decades. Explain how a virus might cause cancer.
7. A tumor is removed from a mouse and broken up into cells. Each cell is injected into a different mouse. Although all the mice used in the experiment are genetically identical and raised in the same environment, the animals develop cancers with different rates of metastasis. Some mice die quickly, some linger, and others recover. What do these results indicate about the characteristics of the original tumor cells?
8. Colon, breast, ovarian, and stomach cancers can be prevented by removing the affected organ. Why is this approach not possible for chronic myeloid leukemia?
9. A vegetarian develops pancreatic cancer and wants to sue the nutritionist who suggested she follow a vegetarian diet. Is her complaint justified? Why or why not?
10. MammaPrint is a DNA microarray-based test of the expression of 70 genes implicated in breast cancer. Certain patterns are significantly more common in cancers that spread, creating a "signature" that doctors can use to guide treatment decisions. Cite an advantage and a shortcoming of this test.
11. The discovery of cancer stem cells suggests a new type of treatment—develop a drug that stops self-renewal. Explain how such a drug might work, and what an adverse effect might be.
12. Colorectal cancer is diagnosed in half a million people worldwide each year.

In 4 percent of diagnosed individuals, the cancer is part of a familial cancer syndrome, such as Lynch syndrome (OMIM 114400). Genetic testing for Lynch syndrome targets mismatch repair genes, and costs about \$3,000. What information would be valuable to decide if it is practical to test for Lynch syndrome for all cases of newly diagnosed colon cancer?

13. A mutation in a gene called *FLT3*, which encodes a tyrosine kinase receptor, causes acute myelogenous leukemia, which has a five-year survival rate of 20 percent. A new drug blocks the receptor on white blood cells. Explain how it works.

### Web Activity

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 18**, and **Web Activities** to find the website link needed to complete the following activity.

14. Go to the Cancer Quest website. Click on one oncogene and one tumor suppressor, and describe how, when mutant, they cause cancer.
15. Consult the websites for the pharmaceutical companies that market

Herceptin, Gleevec, Avastin, or any other cancer drug and explain how the drug works.

16. A test called OncoPlan can predict if a breast, colon, or stomach cancer is likely to recur after surgery. Results are used to decide if a patient is likely to benefit from chemotherapy after surgery. Specifically, the test examines levels of two related proteins, called tyr-phosphorylated Shc and p66 Shc. Results of a study indicated that patients whose tumors had low levels of p66 Shc and had chemotherapy had twice the survival rate of patients whose tumors had low levels of p66 Shc and did not have chemotherapy, but chemotherapy did not benefit patients who had high levels of p66 Shc. The company's website (<http://www.catalystoncology.com>) has further information. If you had cancer and your physician suggested that you have this test, what questions would you ask before consenting to take it?

### Case Studies and Research Results

17. Elsie finds a small lump in her breast and goes to her physician, who takes a medical and family history. She mentions that her father died of brain cancer, a cousin had

leukemia, and her older sister was just diagnosed with a tumor of connective tissue. The doctor assures her that the family cancer history doesn't raise the risk that her breast lump is cancerous, because the other cancers were not in the breast. Is the doctor correct?

18. Lung cancer is classified as "small cell" or "non-small cell" based on the appearance of cancer cells under a microscope. However, non-small cell lung cancers fall into three subgroups, based on gene expression patterns. Suggest two ways that this information might be used.
19. A study of 32,000 patients in a cancer registry in Iceland identified six cancers as being more common among blood relatives of patients compared to the general population, as well as three cancers that were more common among the spouses of patients. How do these two groups of cancers differ in terms of the relative contributions of genes versus environmental influences?

## A Second Look

1. Why was the author not concerned about passing on her thyroid cancer to her children?
2. Was the physician testing for an oncogene or a tumor suppressor?
3. How can gene expression profiling make cancer treatment safer?

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

Li-Fraumeni syndrome  
Multiple endocrine neoplasia  
Cancer stem cells



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Genetic Technologies: Amplifying, Modifying, and Monitoring DNA

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- 19.2 **Amplifying DNA**
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  - Transgenic Plants
  - Genetically Modified Animals
- 19.4 **Monitoring Gene Function**
  - Tracking the Aftermath  
of Spinal Cord Injury
  - Solving a Problem:  
Interpreting a DNA  
Sequence Variation
  - Microarray

## A BRIEF HISTORY OF CHEESE

Once upon a time, a weary nomad wandering a middle Eastern desert stopped to take a sip of milk from a saddlebag made from the fourth stomach of a calf. He discovered, instead of milk, tasty solids suspended in a thin liquid. This must have happened more than once, and when people realized that the white solids tasted good and lasted for long journeys, cheese was born.

The story of the discovery of cheese likely happened about 6,000 B.C. By 1184 B. C., the Greeks were using milk from goats and sheep to make a cheese that was probably similar to feta, and by the third century B.C., they were making horse cheese. Written records trace the origins of various modern cheeses—gorgonzola from 879 A.D., roquefort from 1070 A.D., and cheddar from around 1500 A.D.

Cheesemaking is a simple chemical reaction. A mixture of enzymes breaks down the milk protein casein into curds (solid) and whey (liquid). The most powerful enzyme, chymosin, breaks casein in two. The first segment becomes the curds that can go on to become cheese, and the second segment is the whey.

Traditionally, chymosin to make cheese was extracted from ground-up calf stomachs soaked in saltwater and vinegar, either fresh or frozen. Or synthetic chemicals coagulate milk, but produce an inferior tasting cheese, as do enzymes from plants, microorganisms, or molds. Biotechnology provided a better way to make cheese: the gene that encodes chymosin is placed into the genome of a filamentous fungus, *Aspergillus niger*, which then produces the enzyme. The genetically modified cheese is cheaper to produce, doesn't require killing calves (pleasing cows and vegetarians), and imparts better flavor to aged cheeses.



Cheese-making requires an enzyme from calf stomachs—unless fungus is genetically modified to make it.



## 19.1 Patenting DNA

**Biotechnology** is the use or alteration of cells or biological molecules for specific applications. It is an ancient art as well as a modern science. Using yeast to ferment fruit or produce wine are biotechnologies, as is extracting biochemicals from organisms.

The popular terms “genetic engineering” and “genetic modification” refer broadly to any biotechnology that manipulates genetic material. This includes altering the DNA of an organism to suppress or enhance the activities of its own genes, as well as combining the genetic material of different species. Organisms that harbor DNA from other species are termed **transgenic** and their DNA is called **recombinant DNA**.

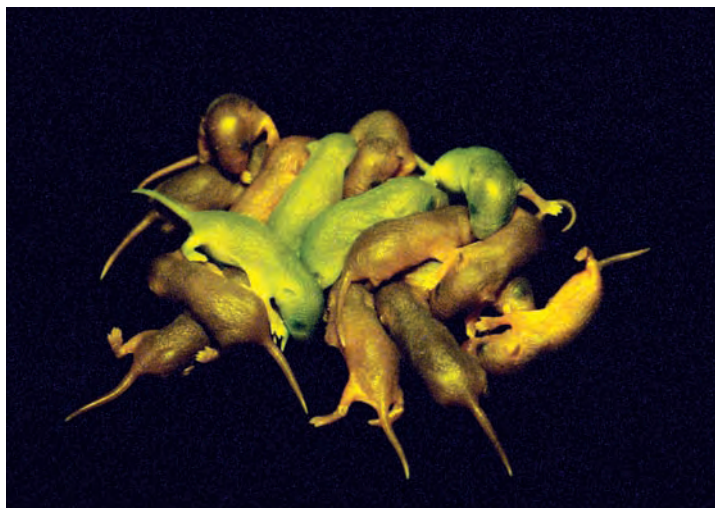
Cells growing in culture can also harbor recombinant DNA, which is how many drugs based on human proteins are manufactured. Some human proteins that are simple peptides without attached sugars can be synthesized in bacterial cells, which are prokaryotic. However, complexly folded proteins and those with attached sugars must be produced in eukaryotic cells. Here, the proteins fold and sugars are attached, as they are in the human body. Cells that harbor recombinant DNA are typically grown at pharmaceutical companies in large containers called bioreactors.

Creating transgenic organisms is possible because all life uses the same genetic code (**figure 19.1**). It is this mixing of DNA from different species that some people object to as being unnatural. In fact, DNA moves and mixes between species in nature—bacteria do it, and it is why we have viral DNA sequences in our chromosomes. But human-instituted genetic modification usually endows organisms with traits they would probably not acquire naturally, such as fish that can tolerate very cold water, tomatoes that grow in salt water, and bacteria that synthesize human insulin.

Transgenic organisms raise legal questions. Is a corn plant that manufactures a protein naturally found only in green beans a patentable invention? To qualify for patent protection, a transgenic organism must be new, useful, and not obvious (see Technology Timeline). Patent law has had to evolve to keep up with modern biotechnology. In the 1980s, when sequencing a gene was painstakingly slow, only a few genes

were patented. Then, in the mid-1990s, with faster sequencing technology and shortcuts to finding the protein-encoding

portions of the genome, the U.S. National Institutes of Health and biotech companies began seeking patent protection for



**Figure 19.1 The universality of the genetic code makes biotechnology possible.** The greenish mice contain the gene encoding a jellyfish’s green fluorescent protein (GFP). Researchers use GFP to mark genes of interest. The GFP mice glow less greenly as they mature and more hair covers the skin. The non-green mice are not genetically modified.

## Technology Timeline

### Patenting Life and Genes

1790	U.S. patent act is enacted. An invention must be new, useful, and not obvious to earn a patent.
1873	Louis Pasteur is awarded first patent on a life form, for yeast used in industrial processes.
1930	New plant variants can be patented.
1980	First patent is awarded on a genetically modified organism, a bacterium given four plasmids (DNA rings) that enable it to metabolize components of crude oil. The plasmids are naturally occurring, but do not all occur naturally in a single type of bacterium.
1988	First patent is awarded for a transgenic organism, a mouse that manufactures human protein in its milk. Harvard University granted patent for “OncoMouse” transgenic for human cancer.
1992	Biotechnology company is awarded a broad patent covering all forms of transgenic cotton. Groups concerned that this will limit the rights of subsistence farmers contest the patent several times.
1996–1999	Companies patent partial gene sequences and certain disease-causing genes as the basis for developing specific medical tests.
2000	With gene and genome discoveries pouring into the Patent and Trademark Office, requirements tightened for showing utility of a DNA sequence.
2003	Attempts to enforce patents on nonprotein-encoding parts of the human genome anger researchers who support open access to the information.
2007	Patent requirements must embrace new, more complex definition of a gene.

thousands of short DNA sequences, even if their functions weren't known. Because of the flood of applications, the U.S. Patent and Trademark Office tightened requirements for utility. Today, with entire genomes being sequenced in the time it once took to decipher a single gene, a DNA sequence alone does not warrant patent protection. The described molecule must be useful as a tool for research or as a novel or improved product.

Despite the increasing stringency of patent requirements, problems still arise concerning the status of DNA sequences. A biotechnology company in the United States, for example, holds a patent on the *BRCA1* breast cancer gene that includes any diagnostic tests based on the DNA sequence. That company's tests, however, do not cover all mutations in the gene. A French physician working with a family that has a unique large deletion is challenging the patent, because to be tested, her patients must pay a high licensing fee to the U.S. company that "owns" the gene sequence.

Analysis of human genome information continues to complicate patenting. One problem is redundancy. For the same gene, it is possible to patent the entire sequence (termed genomic DNA), or just the protein-encoding exons. A researcher can also patent a gene variant, such as a sequence containing a SNP or mutation. A company or researcher developing a tool or test based on a particular gene or its encoded protein might infringe upon several patents that are based on essentially the same information. For example, it is unclear how patents would cover exons common to different genes. Now, as genetics shifts from a gene-by-gene focus to analyzing expression patterns of suites of interacting genes, patent law will have to once again adjust to keep up with scientific developments.

### Key Concepts

1. Biotechnology is the use or modification of cells or biological molecules for a specific application.
2. Patent law regarding DNA has evolved with the technology since the 1970s, and is still changing.

## 19.2 Amplifying DNA

Some forensic and medical tests require many copies of a specific DNA sequence from a small initial sample. In one case, investigators collected a tiny smear of brain tissue on a car fender and had its DNA extracted, sequenced, and compared to DNA from three unidentified headless corpses in a city morgue. The DNA in the brain matter matched one of the bodies, helping to solve the crime.

Mass-producing a DNA sequence is called nucleic acid amplification. Technologies that amplified DNA were invented in the 1970s and 1980s. The first and best known is the **polymerase chain reaction** (PCR), which amplifies but does not change the initial DNA sequence. PCR was used to identify the brain material on the car fender. Producing drugs in bacteria uses another approach, recombinant DNA technology, that amplifies DNA that includes sequences from other types of organisms. PCR is done on molecules; recombinant DNA technology works in cells. Recombinant DNA technology is addressed in the next section.

PCR is based on the natural process of DNA replication. Recall from chapter 9 that every time a cell divides, it replicates all

of its DNA. PCR uses DNA polymerase to rapidly replicate a specific DNA sequence millions of times.

Applications of PCR are eclectic (**table 19.1**). In forensics, it is used routinely to amplify DNA sequences that are profiled to establish blood relationships, to identify remains, and to help convict criminals or exonerate the falsely accused. In agriculture, veterinary medicine, environmental science, and human health care, PCR amplifies the DNA or RNA of pathogens to detectable levels. In genetics, PCR is both a crucial laboratory tool to identify genes and it is a component of many diagnostic tests.

PCR was born in the mind of Kary Mullis on a moonlit night in northern California in 1983. As he drove the hills, Mullis was thinking about the precision of DNA replication, and a way to tap into it popped into his mind. He excitedly explained his idea to his girlfriend and then went home to think it through. "It was difficult for me to sleep with deoxyribonuclear bombs exploding in my brain," he wrote much later.

The idea behind PCR was so simple that Mullis had trouble convincing his superiors at Cetus Corporation that he was onto something. Over the next year, he used the technique to amplify a well-studied gene.

Table 19.1

### Uses of PCR

PCR has been used to amplify DNA from:

- a cremated man, from skin cells left in his electric shaver, to diagnose an inherited disease in his children.
- human tissue from the site of the World Trade Center in the days following September 11, 2001, to identify victims.
- a preserved quagga (a relative of the zebra) and a marsupial wolf, both extinct.
- microorganisms that cannot be cultured for study.
- the brain of a 7,000-year-old human mummy.
- the digestive tracts of carnivores, to reveal food web interactions.
- roadkills and carcasses washed ashore, to identify locally threatened species.
- products illegally made from endangered species, such as powdered rhinoceros horn, sold as an aphrodisiac.
- genetically altered bacteria that are released in field tests, to follow their dispersion.
- one cell of an 8-celled human embryo to detect a disease-related genotype.
- poached moose meat in hamburger.
- remains in Jesse James's grave, to make a positive identification.
- the guts of genital crab lice on a rape victim, which matched the DNA of the suspect.
- dried semen on a blue dress belonging to a White House intern.
- fur from Snowball, a cat that linked a murder suspect to a crime.

After convincing his Cetus colleagues Mullis published a landmark 1985 paper and filed patent applications, launching the field of nucleic acid amplification. Mullis received a \$10,000 bonus for his invention, which the company sold to another for \$300 million. Mullis did, however, win a Nobel prize.

PCR rapidly replicates a selected sequence of DNA in a test tube (**figure 19.2**). The requirements include:

1. Knowing parts of a target DNA sequence to be amplified.
2. Two types of lab-made, single-stranded, short pieces of DNA called primers. These are complementary in sequence to opposite ends of the target sequence.
3. A large supply of the four types of DNA nucleotide building blocks.
4. Taq1, a DNA polymerase produced by *Thermus aquaticus*, a microbe that inhabits hot springs. This enzyme is adapted to its host's hot surroundings and makes PCR easy because it does not fall apart when DNA is heated, as most proteins do.

In the first step of PCR, heat is used to separate the two strands of the target DNA.

Next, the two short DNA primers and Taq1 DNA polymerase are added. The temperature is lowered. Primers bind by complementary base pairing to the separated target strands. In the third step, the Taq1 DNA polymerase adds bases to the primers and builds a sequence complementary to the target sequence. The newly synthesized strands then act as templates in the next round of replication, which is initiated immediately by raising the temperature. All of this is done in an automated device called a thermal cycler, or in a device that uses microscopic layers of heated and cooled silicon, to control the key temperature changes. The heat-resistant DNA polymerase is crucial to the process.

The pieces of identical DNA accumulate exponentially. The number of amplified pieces of DNA equals  $2^n$ , where  $n$  equals the number of temperature cycles. After just 20 cycles, 1 million copies of the original sequence have accumulated in the test tube.

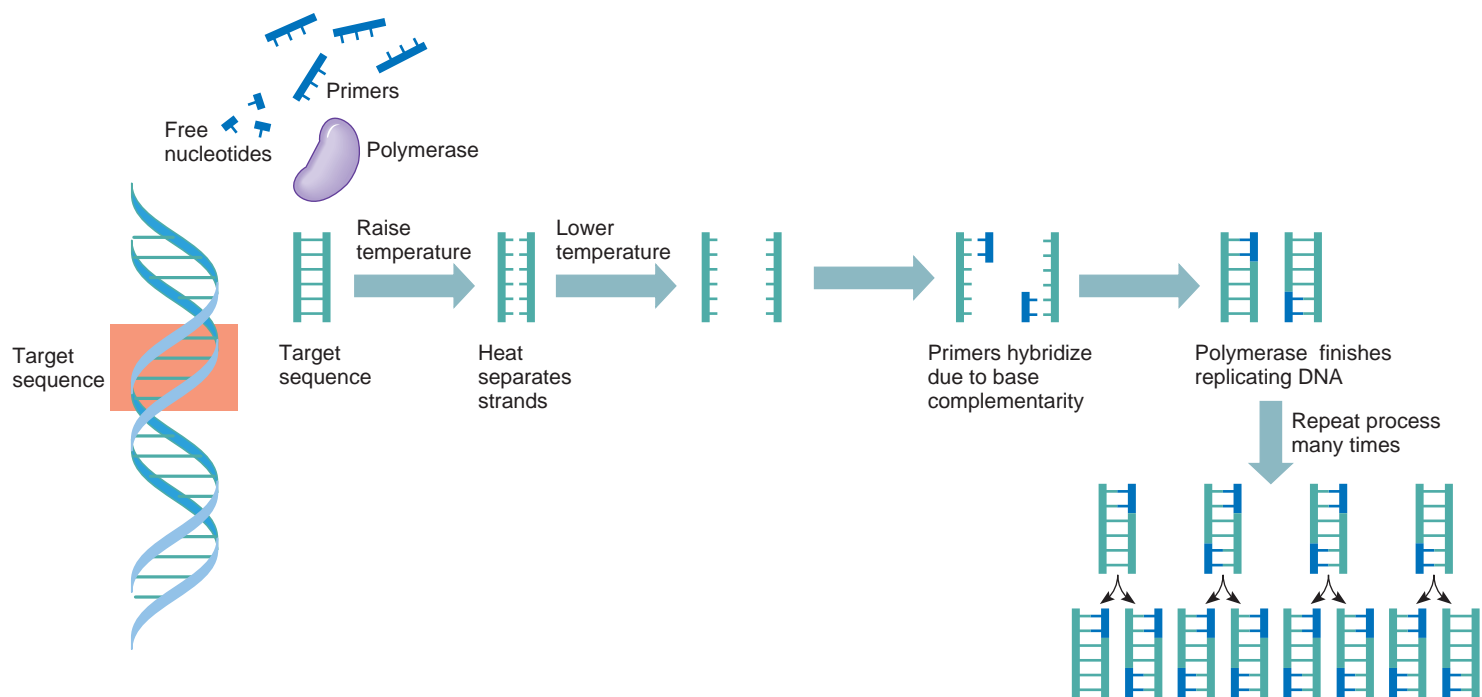
PCR's greatest strength is that it works on crude samples of rare, old, and minute sequences. PCR's greatest weakness, ironically, is its exquisite sensitivity. A blood sample submitted for diagnosis of an infection, if contaminated by leftover DNA from a previous test, or a stray eyelash from the person running the reaction, can yield a false result.

Using layered silicon instead of a thermal cycler to amplify DNA greatly speeds PCR. Thirty cycles using the thermal cycler take ninety minutes; with the silicon layers, it takes a little over four minutes. The speed is valuable in situations where rapid diagnosis is important, such as the case of a person with a life-threatening infection who requires the right antibiotic, or on a battlefield to detect biological weapons.

The invention of PCR inspired other nucleic acid amplification techniques. One is transcription-mediated amplification, which copies target DNA into RNA and then uses RNA polymerase to amplify the RNA. This procedure doesn't require temperature shifts, and it generates 100 to 1,000 copies per cycle, compared to PCR's doubling, and can yield 10 billion copies of a selected sequence in a half hour!

## Key Concepts

1. PCR rapidly replicates a short DNA sequence.
2. PCR has many uses.
3. Other nucleic acid amplification technologies followed PCR.



**Figure 19.2 Amplifying a specific DNA sequence.** In the polymerase chain reaction, specific primers along with a thermostable DNA polymerase and plenty of free nucleotides are used to replicate a DNA sequence of interest. The reaction rapidly builds up millions of copies of the target sequence. Figure 14.9 shows an application of PCR.



## 19.3 Modifying DNA

Recombinant DNA technology adds genes from one type of organism to the genome of another. It was the first gene modification biotechnology, and was initially done in bacteria. When bacteria bearing recombinant DNA divide, they yield many copies of the “foreign” DNA, and under proper conditions they produce many copies of the protein that the foreign DNA specifies. Recombinant DNA technology is also known as gene cloning. “Cloning” in this context refers to making many copies of a specific DNA sequence.

### Recombinant DNA

Researchers first began pondering the potential uses and risks of mixing DNA from different species in the 1970s. In February 1975, 140 molecular biologists convened at Asilomar, on California’s Monterey Peninsula, to discuss the safety and implications of a new type of experiment. Investigators had found a simple way to combine the genes of two species, and they were concerned about the safety of experiments requiring the use of a cancer-causing virus, and about where the field was headed. They discussed restricting the types of organisms used in recombinant DNA research and explored ways to prevent escape of a resulting organism from the laboratory. The guidelines drawn up at Asilomar outlined measures of “physical containment,” such as using specialized hoods and airflow systems that would keep the organisms inside the laboratory, and “biological containment,” such as weakening organisms so that they could not survive outside the laboratory.

A decade after the Asilomar meeting, many members of the original group reconvened at the meeting site to assess progress. Nearly all agreed on two points: Recombinant DNA technology was safer than expected, and the technology had spread to industry more swiftly and in more diverse ways than anyone had imagined. At a meeting twenty-five years after the original event, attendees concluded that biotechnology had become so commercialized that the open atmosphere of the original gathering was no longer possible.

Recombinant DNA-based products have been slow to reach the marketplace because of the high cost of the research and the long

time it takes to develop any new drug. Today, several dozen such drugs are available, and more are in the pipeline. Recombinant DNA research initially focused on direct gene products such as peptides and proteins, such as insulin, growth hormone, and clotting factors. However, the technology can target carbohydrates and lipids by affecting the genes that encode enzymes required to synthesize them.

### Constructing Recombinant DNA Molecules—An Overview

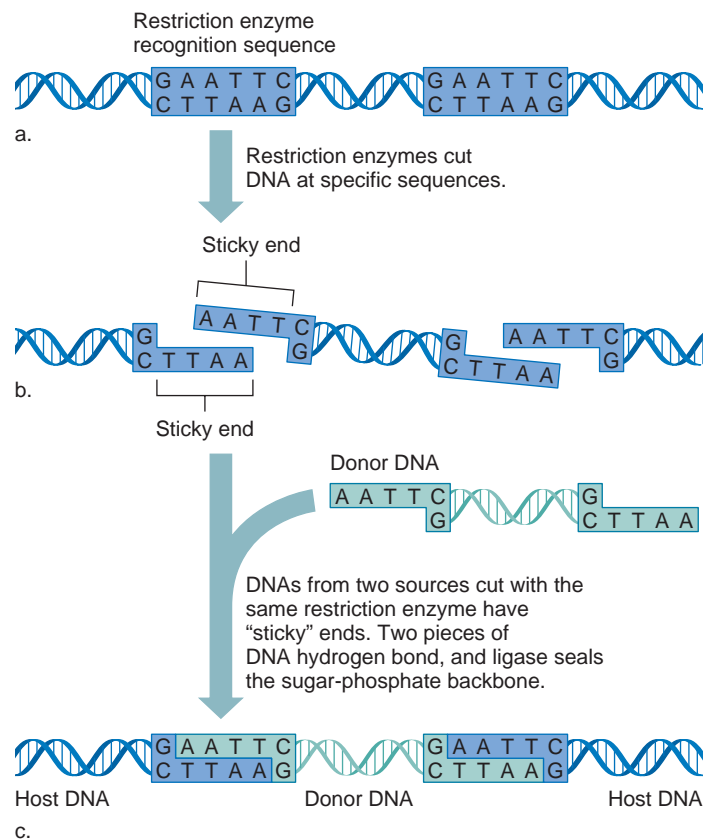
Manufacturing recombinant DNA molecules requires restriction enzymes that cut donor and recipient DNA at the same sequence; DNA to carry the donor DNA (called cloning vectors); and recipient cells (bacteria or other cultured single cells).

After inserting donor DNA into vectors, the procedure requires several steps:

- Selecting cells where the genetic material includes foreign DNA

- Selecting cells that received the gene of interest
- Stimulating transcription of the foreign gene and translation of its protein product
- Collecting and purifying the desired protein

The natural function of restriction enzymes is to protect bacteria by cutting DNA of infecting viruses. Methyl ( $\text{CH}_3$ ) groups shield the bacterium’s own DNA from its restriction enzymes. Bacteria have hundreds of types of restriction enzymes. Some of them cut DNA at particular sequences of four, five, or six bases that are symmetrical in a specific way—the recognized sequence reads the same, from the 5′ to 3′ direction, on both strands of the DNA. For example, the restriction enzyme EcoRI, shown in **figure 19.3**, cuts at the sequence GAATTC. The complementary sequence on the other strand is CTTAAG,



**Figure 19.3 Recombining DNA.** A restriction enzyme makes “sticky ends” in DNA by cutting it at specific sequences. **(a)** The enzyme EcoRI cuts the sequence GAATTC between G and A. **(b)** This staggered cutting pattern produces “sticky ends” of sequence AATT. The ends attract through complementary base pairing. **(c)** DNA from two sources is cut with the same restriction enzyme. Pieces join, forming recombinant DNA molecules.

which, read backwards, is GAATTC. (You can try this with other sequences to see that it rarely works this way.) In the English language, this type of symmetry is called a palindrome, referring to a sequence of letters that reads the same in both directions, such as “Madam, I’m Adam.” Palindromic sequences in DNA include sequences on complementary strands.

The cutting action of some restriction enzymes on double-stranded DNA creates single-stranded extensions. They are called “sticky ends” because they are complementary to each other and as a result form hydrogen bonds as their bases pair. Restriction enzymes work as molecular scissors in creating recombinant DNA molecules because they cut at the same sequence in any DNA source. That is, the same sticky ends result from the same restriction enzyme, whether the DNA is from a mockingbird or a maple.

Another natural “tool” used in recombinant DNA technology is a cloning vector. This structure carries DNA from the cells of one species into the cells of another. A vector can be any piece of DNA into which other DNA can insert. A commonly used type of vector is a **plasmid**, which is a small circle of double-stranded DNA that occurs naturally in some bacteria, yeasts, plant cells, and other types of organisms (**figure 19.4**). Viruses that infect bacteria, called bacteriophages, are another type of vector. Bacteriophages are manipulated to transport DNA but not cause disease. Disabled retroviruses are used as vectors too, as are artificial chromosomes from bacteria and yeast. Bacterial artificial chromosomes (BACs) were used to sequence the human genome.

When choosing a cloning vector, size matters. The desired gene must be short enough to insert into the vector. Gene size is typically measured in kilobases (kb), which are thousands of bases. **Table 19.2** lists the capacities of several cloning vectors.

To create a recombinant DNA molecule, a restriction enzyme cuts DNA from a donor cell at sequences known to bracket the gene of interest (**figure 19.5**). The enzyme leaves single-stranded ends on the cut DNA, each bearing a characteristic base sequence. Next, a plasmid is isolated and cut with the same restriction enzyme used to cut the donor DNA. Because the same restriction enzyme



**Figure 19.4 Plasmids.** Plasmids are small circles of DNA found naturally in the cells of some organisms. A plasmid can replicate independent of the host genetic material, including any DNA inserted into it. For this reason, plasmids make excellent cloning vectors. Plasmids used as vectors have restriction enzyme cutting sites and antibiotic resistance genes, both of which are useful in transferring DNA and then detecting it.

**Table 19.2**  
Cloning Vectors

Vector	Size of Insert Accepted (kb)
Plasmid	up to 15
Bacteriophage	up to 90
Bacterial artificial chromosome (BAC)	100–500
Yeast artificial chromosome (YAC)	250–2,000

cuts both the donor DNA and the plasmid DNA, the same complementary single-stranded base sequences extend from the cut ends of each. When the cut plasmid and the donor DNA are mixed, the single-stranded sticky ends of some plasmids base pair with the sticky ends of the donor DNA. The result is a recombinant DNA molecule, such as a plasmid carrying the human insulin gene. The plasmid and its human gene can now be transferred into a cell, typically bacterial.

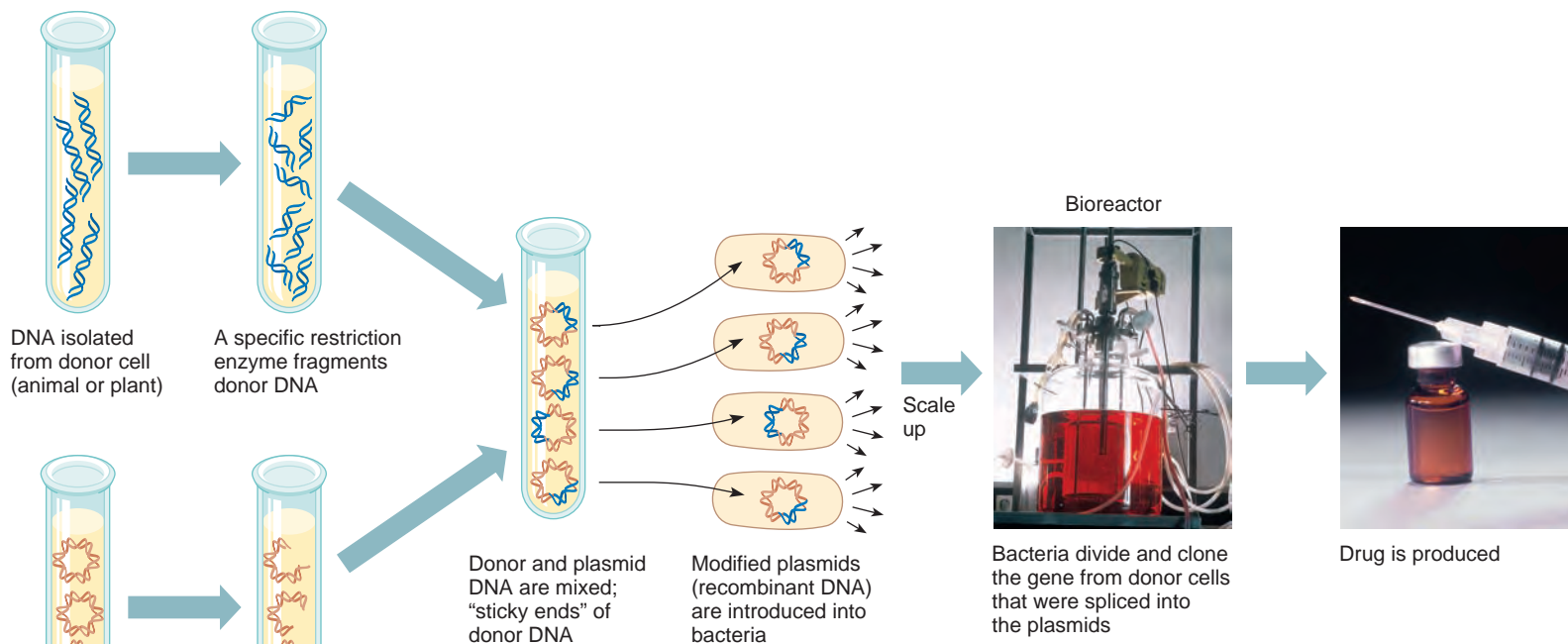
### Isolating the Gene of Interest

Constructing recombinant DNA molecules usually begins by cutting all of the DNA of the donor cell. This DNA, which includes non-protein-encoding sequences, is termed genomic DNA. Researchers assemble collections of recombinant bacteria (or other single cells) that harbor pieces of a genome. By using several copies of a genome, the pieces overlap where sequences align. Such a collection is called a **genomic library**. For each application, such as using a human protein as a drug, a particular piece of DNA must be identified and isolated from a genomic library. There are several ways to do this “needle in a haystack” type of search.

A piece of DNA that is complementary to part of the template strand of the gene in question can be linked to a label, such as a radioactive or fluorescent molecule. This labeled gene fragment is called a **DNA probe**. It emits a signal when it binds to its complement in a cell that contains a recombinant plasmid. DNA probes can also be made using genes of similar sequence from other species—they will bind the human version of the gene. Using such a probe is a little like mistakenly using hipopotamus to search for hippopotamus on the Internet. You’d probably still come up with a hippo.

A genomic library contains too much information for a researcher seeking a particular protein-encoding gene—it may also contain introns, the genes that encode rRNAs and tRNAs, and many repeated sequences. A shortcut is to use another type of library, called a complementary DNA, or **cDNA library**, that represents only protein-encoding genes. A cDNA library is made from the mRNAs in a differentiated cell, which represent the proteins manufactured there. For example, a muscle cell has abundant mRNA that encodes contractile proteins, whereas a fibroblast has many mRNAs that represent connective tissue proteins.

To make a cDNA library, researchers first extract the mRNAs from cells. Then, these RNAs are used to construct complementary or “c” DNA strands using reverse transcriptase, DNA nucleotide triphosphates, and DNA polymerase (**figure 19.6**). Reverse



**Figure 19.5 Recombinant DNA.** To construct a recombinant DNA molecule, DNA isolated from a donor cell and a plasmid are cut with the same restriction enzyme and mixed. Some of the sticky ends from the donor DNA hydrogen bond with the sticky ends of the plasmid DNA, forming recombinant DNA molecules. When such a modified plasmid is introduced into a bacterium, it is mass produced as the bacterium divides.

transcriptase synthesizes DNA complementary to RNA. DNA polymerase and the nucleotides then can synthesize the complementary strand to the single-stranded cDNA to form a double-stranded DNA. Different cell types yield different cDNA collections, or libraries, that reflect which genes are expressed. They do not, however, reveal protein abundance because in a cell mRNA molecules are transcribed and degraded at different rates.

A specific cDNA can be taken from a cDNA library and used as a probe to isolate the original gene of interest from the genomic library. If the goal is to harness the gene and eventually collect its protein product, then the genomic version is useful, because it includes control regions such as promoters. Once a gene of interest is transferred to a cell where it can be transcribed into mRNA and that RNA can be translated, the protein is collected. Such cells are typically grown in bioreactors, with nutrients sent in and wastes removed. A researcher collects the desired

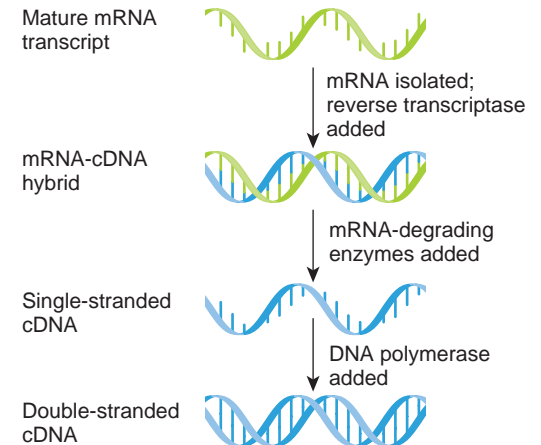
product from the medium the cells are growing in.

### Selecting Recombinant DNA Molecules

Much of the effort in recombinant DNA technology is in identifying and separating cells that contain the gene of interest, once the foreign DNA is inserted into the vector. Three types of recipient cells can result:

1. Cells that lack plasmids
2. Cells that contain plasmids that do not contain a foreign gene
3. Cells that contain plasmids that have picked up a foreign gene (the goal)

The procedure is set up to distinguish bacteria that have taken up recombinant plasmids from those that have not taken up plasmids or that have admitted plasmids that do not carry foreign DNA. One type of strategy consists of two steps: using an antibiotic resistance gene and a color change



**Figure 19.6 Copying DNA from RNA.** Researchers make cDNA from mRNA using reverse transcriptase, an enzyme from a retrovirus. A cDNA version of a gene includes the codons for a mature mRNA, but not sequences corresponding to promoters and introns. Control sequences from bacteria may be added so that the eukaryotic gene can be transcribed and translated in a prokaryote (the bacterium).



reaction to highlight the plasmids that have picked up the gene of interest. First, human and plasmid DNA are cut with the same restriction enzymes and mixed. The plasmids are closed up with ligase (the enzyme that glues the sugar-phosphate backbone when DNA replicates), and transferred to bacterial cells. When the antibiotic is applied, only cells harboring plasmids survive. The plasmids also include a gene that encodes an enzyme that catalyzes a reaction that produces a blue color. If a human gene inserts and interrupts the gene for the enzyme, the bacterial colony that grows is not blue, and is therefore easily distinguished from the blue bacterial cells that have not incorporated the human gene.

When cells containing the recombinant plasmid divide, so does the plasmid. Within hours, the original cell gives rise to many harboring the recombinant plasmid. The enzymes, ribosomes, energy molecules, and factors necessary for protein synthesis transcribe and translate the plasmid DNA and its foreign gene, producing the desired protein.

Products from Recombinant DNA Technology

In basic research, recombinant DNA technology provides a way to isolate individual genes from complex organisms and observe their functions on the molecular level. Recombinant DNA has many practical uses, too. The first was to mass-produce protein-based drugs.

The great advantage of drugs produced using recombinant DNA technology is that they are pure, and they are the human version of the protein. For example, before recombinant DNA technology was invented, human growth hormone came from cadavers, insulin came from pigs and cows, follicle-stimulating hormone came from the urine of post-menopausal women, and clotting factors were pooled from hundreds or thousands of donors—introducing great risk of infection, especially after HIV and hepatitis C became more widespread.

The first drug to be manufactured using recombinant DNA technology was insulin. Before 1982, people with type 1 diabetes mellitus obtained the insulin that they injected daily from pancreases removed from cattle in slaughterhouses. Cattle

insulin is so similar to the human peptide, different in only 2 of its 51 amino acids, that most people with diabetes could use it. However, about 1 in 20 patients is allergic to cow insulin because of the slight chemical difference. Until recombinant DNA technology was developed, the allergic patients had to use expensive combinations of insulin from other animals or human cadavers. A person with diabetes can now purchase “Humulin,” the human protein made in *E. coli*, at a local drugstore. **Table 19.3** lists some drugs produced using recombinant DNA technology.

Drugs developed using recombinant DNA technology must compete with conventional products. Deciding whether a recombinant drug is preferable to an existing similar drug is often a matter of economics, and common sense. For example, interferon  $\beta$ -1b treats a type of multiple sclerosis, but this recombinant drug costs more than \$20,000 per year. British researchers calculated what it would cost to treat the nation’s patients who would benefit from the drug, and then determined how else the funds could be spent. They concluded that more people would be served if the money

were spent on improved supportive care for many rather than on a costly treatment for a few.

Tissue plasminogen activator (tPA), a recombinant clot-busting drug developed in the mid-1980s, also has cheaper alternatives. If injected within four hours of a heart attack, tPA dramatically limits damage to the heart muscle by restoring blood flow. It costs \$2,200 a shot. An older drug, streptokinase, is extracted from unaltered bacteria and is nearly as effective, at \$300 per injection. tPA is very valuable for patients who have already had streptokinase and could have an allergic reaction if they were to use it again. Bioethics: Choices for the Future on page 383 considers another drug derived from recombinant DNA technology, erythropoietin (EPO).

An application of recombinant DNA technology in the textile industry is a new source of indigo, the dye used to make blue jeans blue. The dye originally came from mollusks and fermented leaves of the European woad plant or Asian indigo plant. The 1883 discovery of indigo’s chemical structure led to the invention of a synthetic process to produce the dye using coal-tar.

Table 19.3  
Drugs Produced Using Recombinant DNA Technology

Drug	Use
Atrial natriuretic peptide	Dilates blood vessels, promotes urination
Colony stimulating factors	Help restore bone marrow after marrow transplant; restore blood cells following cancer chemotherapy
Deoxyribonuclease (DNase)	Thins secretions in lungs of people with cystic fibrosis
Epidermal growth factor	Accelerates healing of wounds and burns; treats gastric ulcers
Erythropoietin (EPO)	Stimulates production of red blood cells in cancer patients
Factor VIII	Promotes blood clotting in treatment of hemophilia
Glucocerebrosidase	Corrects enzyme deficiency in Gaucher disease
Human growth hormone	Promotes growth of muscle and bone in people with very short stature due to hormone deficiency
Insulin	Allows cells to take up glucose in treatment of type 1 diabetes
Interferons	Treats genital warts, hairy cell leukemia, hepatitis C and B, Kaposi sarcoma, multiple sclerosis
Interleukin-2	Treats kidney cancer recurrence
Lung surfactant protein	Helps lung alveoli to inflate in infants with respiratory distress syndrome
Renin inhibitor	Lowers blood pressure
Somatostatin	Decreases growth in muscle and bone in pituitary giants
Superoxide dismutase	Prevents further damage to heart muscle after heart attack
Tissue plasminogen activator	Dissolves blood clots in treatment of heart attacks, stroke, and pulmonary embolism

## The Ethics of Using a Recombinant Drug: EPO

EPO is a hormone produced in the kidneys that is a 165-amino-acid protein plus four carbohydrate chains. When the oxygen level in the blood is too low, cells in the kidneys produce EPO, which travels to the bone marrow and binds to receptors on cells that give rise to red blood cell progenitors. Soon, more red blood cells enter the circulation, carrying more oxygen to the tissues (figure 1).

The value of EPO as a drug became evident after the invention of hemodialysis to treat kidney failure in 1961. This otherwise highly successful treatment also causes severe anemia, because dialysis removes EPO from the blood. Counteracting the

anemia required boosting EPO levels. In 1970, the U.S. government sought ways to mass-produce EPO. But levels of EPO in human plasma are too low to pool from donors. A more likely potential source was people suffering from disorders, such as aplastic anemia and hookworm infection, that caused them to secrete large amounts of EPO in their urine.

In the 1970s, the U.S. government obtained EPO from South American farmers with hookworm infections and Japanese aplastic anemia patients. But was it ethical to obtain a scarce substance from the poor to treat the comparatively wealthy? Then AIDS came. Biochemicals from human body fluids were no longer safe.

Recombinant DNA technology solved the EPO problem. The hormone is produced in hamster kidney cells, which can attach EPO's four carbohydrate groups. Today, EPO is sold under various names to treat anemia in dialysis and AIDS patients and is also given with cancer chemotherapy to avoid the need for transfusions.

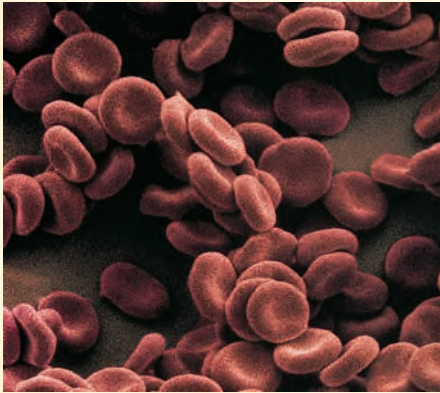
Recombinant EPO found an unexpected market among Jehovah's Witnesses, whose religion forbids transfused blood, which they believe destroys the soul. They can, however, use EPO, because it has been declared a product of recent technology, rather than blood. Some Jehovah's Witnesses have used it before surgery to

boost red blood cell supplies, or afterward to compensate for blood loss.

EPO's ability to increase the oxygen-carrying capacity of blood, and thereby to increase physical endurance, has attracted the attention of competitive athletes. Training at high altitudes increases endurance, and the reason is EPO. The scarcer oxygen in the air at high altitudes stimulates the kidneys to produce EPO, which stimulates production of more red blood cells. Since the early 1990s, athletes have abused EPO to reproduce this effect. A few Dutch bicyclists developed dangerous blood clots in their legs from taking too much of the hormone. Olympic athletes are now routinely screened for EPO abuse.

One large Scandinavian family, however, gets its extra EPO naturally. They have an inherited condition, benign erythrocytosis (OMIM 263400), in which they overproduce the hormone. One of them won a gold medal for skiing in the Olympics. However, athletes who abuse EPO raise the issue of how to control the use of an otherwise valuable drug derived from biotechnology.

EPO is not the only abused biotech-derived drug. Body builders abuse a recombinant version of the hormone somatotropin, used to treat AIDS wasting syndrome, and the Internet is full of ads for recombinant human growth hormone.



**Figure 1** These red blood cells are mass-produced in a patient treated with erythropoietin (EPO).

That method has dominated the industry, but it releases toxic by-products.

In 1983, microbiologists discovered that *E. coli*, with a little help, can produce indigo. The bacterium converts glucose to the amino acid tryptophan, which then forms indole, a precursor to indigo. Another type of bacterium takes the indole to indigo. Researchers altered *E. coli* to suppress the alternative pathways for metabolizing glucose, allowing the cells to synthesize excess tryptophan. They then added genes from the other bacterial species, extending the biochemical pathway all the

way to produce indigo. The result: common bacteria that manufacture the blue dye of denim jeans from glucose, a simple sugar.

### Transgenic Plants

Expressing recombinant DNA in the cells of multicellular organisms is complicated in different ways from expressing human DNA in bacterial cells. Individual organisms must develop and be bred to yield homozygotes if recessive traits are being followed. Dominant traits would be present in

the initial generation. The added or altered characteristic in the multicellular transgenic organism is usually a visible and valued trait or an unusual secretion.

A transgenic plant is easier to create than a transgenic animal because a plant can be derived from somatic cells. A new plant can be grown from a cutting; animal development does not work this way. On the other hand, different vectors and gene transfer techniques are sometimes used in plants because their cell walls, not present in animal cells, are difficult to penetrate. Some manipulations are done on plant cells that



have had their cell walls removed. These denuded plant cells are called protoplasts.

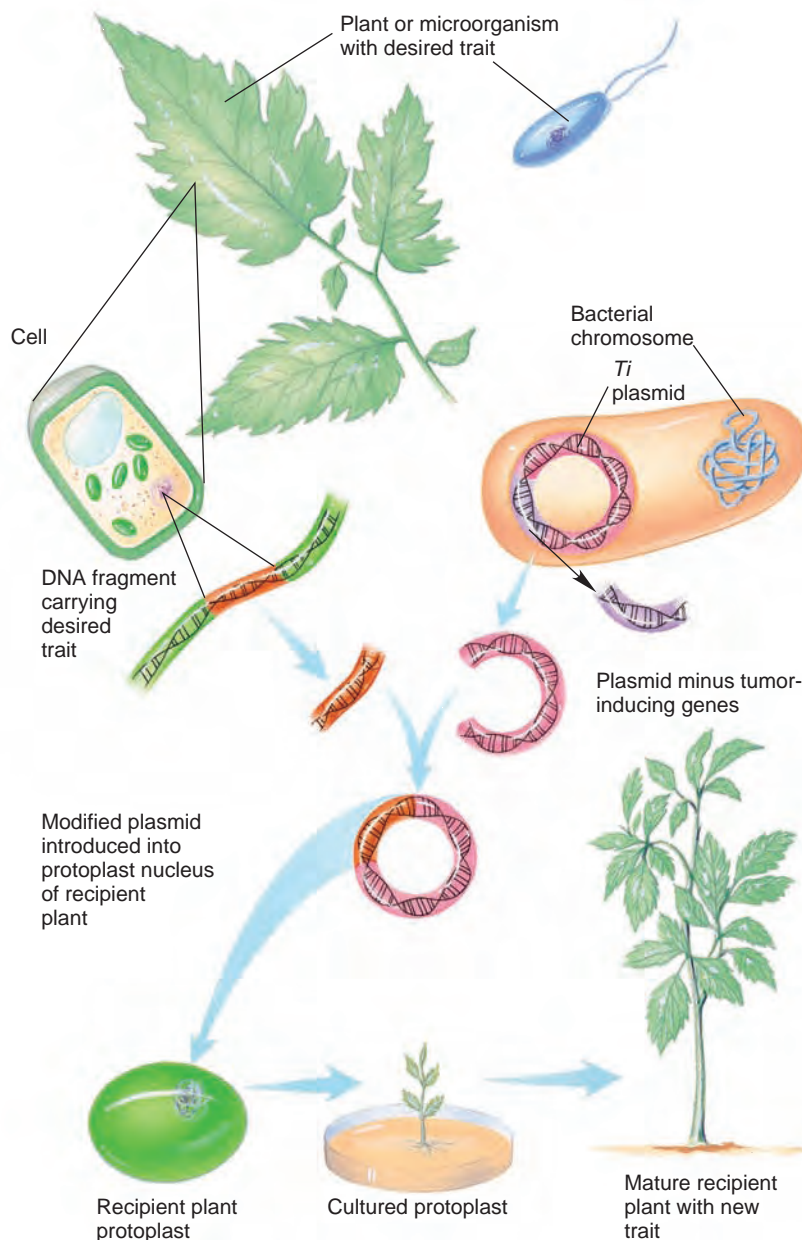
A commonly used plant vector is a *Ti* plasmid (for “tumor-inducing”), which occurs naturally in the bacterium *Agrobacterium tumefaciens* (figure 19.7). A *Ti* plasmid normally causes a tumorlike growth; researchers remove the genes controlling this process. For example, a gene from the bacterium *Bacillus thuringiensis* (*bt*) specifies a protein that destroys the stomach linings of certain insect larvae. When the *bt* gene is introduced into corn cells via a *Ti* plasmid, the cells regenerate corn plants that produce their own insecticide. More than two-thirds of the corn plants grown in the United States are transgenic for the *bt* insecticide gene.

The same gene is used to protect trees such as larch, white spruce, and pioneer elm from gypsy moth and forest tent caterpillars. Use of *bt* protein as a natural insecticide isn’t new—organic farmers have been using the protein for years, applying unmodified bacteria directly to plants. A transgenic plant’s leaves, which are the parts that many insects eat, contain the *bt* insecticide. Transgenic plants are also created whose seeds store proteins useful as drugs, or whose roots secrete useful substances. Table 19.4 lists some useful transgenic plants, and table 19.5 describes some agricultural challenges that transgenic crops can address.

Transgenic plants acquire their new capabilities quickly, in one generation. In contrast, obtaining crops with valuable characteristics using traditional agriculture may require breeding plants through several generations of specific genetic crosses. The recombinant DNA route is also more precise than traditional breeding because it deals with one characteristic at a time, rather than having to follow traits that reassort during meiosis in traditional agriculture.

The creation of a transgenic plant follows these general steps:

1. A gene that confers an agriculturally useful characteristic is isolated and inserted into a cloning vector.
2. The recombinant vector is selected and delivered into protoplasts.
3. Whole plants are regenerated from genetically altered cells, perpetuating the change in all cells.



**Figure 19.7 Producing a transgenic plant.** A DNA fragment carrying the desired gene—conferring resistance to an herbicide, for example—is isolated from its natural source and spliced into a *Ti* plasmid with the tumor-inducing genes removed. The plasmid incorporating the foreign DNA then invades a cell of the recipient plant, entering the nucleus and integrating into the plant’s DNA. Finally, in culture, the cell is regenerated into a mature transgenic plant that expresses the desired trait and passes it on to its progeny. A breeding step may be necessary to obtain plants homozygous for a recessive trait.

4. If the trait is recessive, crosses are set up to generate homozygous recessive plants.
5. The transgenic plants are tested in the laboratory to see if the desired protein is manufactured, and if the introduced

gene (a transgene) is passed on to the next generation.

6. The plants are field-tested to see if the desired trait persists, if the crops affect the ecosystem, and if the crops grow beyond the ecosystem.



Table 19.4

## Genetically Modified Crops

Altered Plant	Effect
Rice with beta carotene and extra iron	Added nutritional value
Canola with high-laurate oil	Can be grown domestically; less costly than importing palm and coconut oils
Delayed ripening tomato	Extended shelf life
Herbicide-resistant cotton	Herbicide kills weeds without harming crop
Minipeppers	Improved flavor, fewer seeds
Bananas resistant to fungal infection	Extended shelf life
Delayed-ripening bananas and pineapples	Extended shelf life
Elongated sweet pepper	Improved flavor, easier to slice
Altered cotton fiber	“Plasticized” fabric
Altered paper pulp trees	Paper component (lignin) easier to process
High-starch potatoes	Absorb less oil when fried
Pest-resistant corn	Can resist European corn borer
Seedless minimelons	Single serving size
Sweet peas and peppers	Retain sweetness longer
Sugarcane with corn gene	Resists bacterial and fungal toxins

Table 19.5

## Potential Benefits and Risks of GM Crops

## Benefits/Applications

1. Greater control than traditional agriculture because single traits (genes) are manipulated.
2. Enhanced nutritional qualities, including added vitamins, minerals, and nutrients that protect against cancer. Increase in nutrients that are absent, scarce, or in inedible parts of the plant.
3. Resistance to pests, diseases, and environmental extremes.
4. Delayed fruit ripening to extend shelf life.
5. Delayed potato development to reduce need for chemicals to suppress sprouting.
6. Elimination of allergens.
7. Production of pharmaceuticals and edible vaccines.
8. Bioremediation of toxins and explosives.
9. Production of biodegradable plastics.
10. Changes in proteins, fats, and carbohydrates that serve as raw materials for paper, lubricants, detergents, food, and many other products.
11. Control of plant height, flowering time, seed size and number, solids content and other traits important for harvesting and processing.
12. Ease of separation of transgenic plant seed from weed seeds.
13. Produce more of the edible portion of a plant.
14. Contribute less phosphorus to animal feces, making groundwater contamination less likely to cause algal blooms.

## Risks

1. “Escape” of transgene beyond field.
2. Economic and political repercussions of displaced traditional products.
3. Harm to farmers and U.S. companies as other nations boycott GM products.
4. Unexpected results from combinations of genes from different species.
5. Inability to predict long-term consequences of introducing GM organisms into the environment.
6. Reduction of biodiversity.

## Genetically Modified Animals

Eukaryotic cells growing in culture are generally better at producing human proteins than are prokaryotic cells such as bacteria. An even more efficient way to express some recombinant genes is in a body fluid of a transgenic animal, such as milk. The fact that the cells secreting the human protein are part of an animal more closely mimics the environment in the human body.

Transgenic sheep, cows, and goats have all expressed human genes in their milk, including those that encode clotting factors, clot busters, and collagen (**table 19.6**). Production of human antibodies in farm animal milk illustrates the value of transgenic animals. Recall from figure 17.12 that antibodies are assembled from the products of several genes—it is quite complex. Antibodies can be produced in mammary gland cells. Researchers attach the appropriate human antibody genes to promoters for milk proteins. (Recall from chapter 10 that a promoter is a short sequence at the start of a gene that controls the rate of transcription.) These promoters normally oversee production of abundant milk proteins. The mammary gland cells of transgenic animals can assemble antibody parts to secrete the final molecules—just as if they were being produced in a developing B cell in the human immune system.

One company that specializes in “transgenic pharming” uses goats, because they have a short breeding cycle and very high milk yield. A liter of milk can yield 1 to 10 grams of a therapeutic protein, which is ten times the yield from an equal volume of cultured cells. The type of animal most often modified to carry human genes, however, is the mouse. Many human diseases have mouse models.

Creating transgenic animals is more challenging than working with plants because of fundamental differences in early development. Several techniques are used to insert DNA into animal cells, including:

- chemicals to open transient holes in plasma membranes
- liposomes (fatty bubbles) to carry DNA into cells as plasma membranes envelop them

Table 19.6

## Products from Transgenic Animals

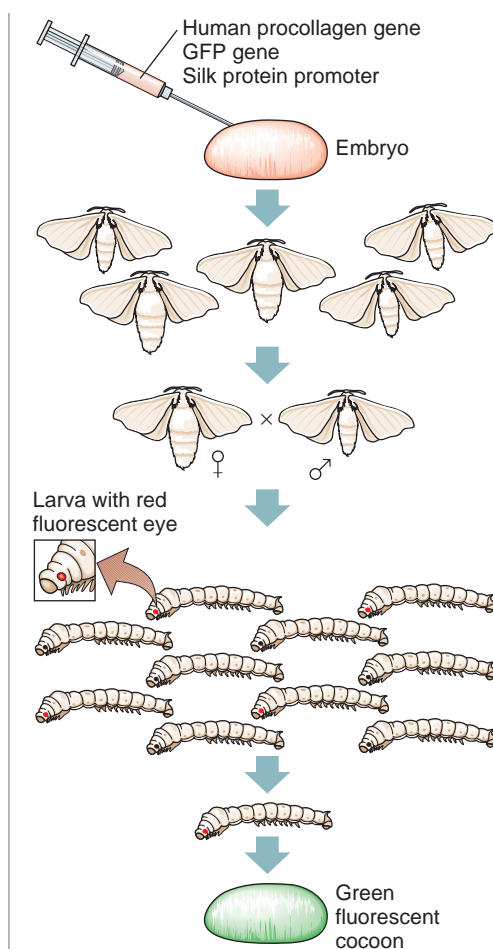
Host	Product	Potential Use
Cows	Lactoferrin	Added to infant formula to bind iron and prevent bacterial infection
Goats	tPA	Breaks up blood clots
Pigs	Hemoglobin	Acts as a blood substitute
Rabbit	Erythropoietin	Treats anemia from dialysis
Rat	Human growth hormone	Treats pituitary dwarfism
Sheep	Alpha-1 antitrypsin	Treats hereditary emphysema

- brief jolts of electricity (electroporation) to open transient holes in plasma membranes
- microscopic needles to inject DNA into cells (microinjection)
- shooting tiny metal particles coated with foreign DNA into cells (particle bombardment)

As in plant cells, once foreign DNA is introduced into an animal cell, it must enter the nucleus, replicate along with the cell's own DNA, and be transmitted when the cell divides. Finally, an organism must be regenerated from the altered cell. If the trait is dominant, the transgenic organism must express it in the appropriate tissues at the right time in development. If the trait is recessive, crosses between heterozygotes may be necessary to yield homozygotes that express the trait. Then the organisms must pass the characteristic on to the next generation.

**Figure 19.8** illustrates transgenic silkworms that have been turned into a factory for a human protein, collagen. The silkworm *Bombyx mori* has been cultivated and its silk coveted for nearly five thousand years. About half of a larva's body is devoted to silk production. Two silk glands secrete threads consisting of linked proteins called fibroins. The insect pulls the strands out of its hind-quarters in an elaborate figure-eight pattern, and once these strands hit the air, they harden into silk. Because of unusual mitotic cell division in which DNA replicates but cells do not divide, each cell in a silk gland has 400,000 copies of the genome, enabling the silkworm to build its cocoon rapidly.

To take advantage of the silkworm's mass-production capabilities, researchers injected



**Figure 19.8 Silk with human collagen, courtesy of transgenic silkworms.** Early embryos receive injections of a human procollagen gene linked to a silk protein promoter, as well as to the green fluorescent protein (GFP) gene. The transgenic silkworms also have a red fluorescent protein gene linked to a promoter that causes it to be expressed in larval eyes. Larvae with red eyes make cocoons that include human collagen.

the human collagen gene attached to a silk protein promoter (control sequence), via a vector into early embryo cells of silkworms. In the next generation, when a larva got the hormonal urge to make silk, it would make silk and also human collagen. To mark the proteins, the investigators used GFP, the same jellyfish gene that lights up the mice in figure 19.1. As an added guide, the recombinant DNA also included a gene for red fluorescent protein, but with a promoter that causes it to be expressed in the eye. The researchers selected red-eyed larvae, then separated the human collagen from their cocoons. Collagen is used in cosmetics and in tissue engineering.

## Bioremediation

Recombinant DNA technology and transgenic organisms provide processes as well as products. In **bioremediation**, bacteria or plants with the ability to detoxify certain pollutants are released or grown in a particular area. Natural selection has sculpted such organisms, perhaps as adaptations that render them unpalatable to predators. Bioremediation uses genes that enable an organism to metabolize a substance that, to another species, is a toxin. The technology uses unaltered organisms, and also transfers “detox” genes to other species so that the protein products can more easily penetrate a polluted area.

Nature offers many organisms with interesting tastes. One type of tree that grows in a tropical rainforest on an island near Australia, for example, accumulates so much nickel from soil that slashing its bark releases a bright green latex ooze. This tree can be used to clean up nickel-contaminated soil.

Bioremediation can tap the metabolisms of transgenic microorganisms, sending them into plants whose roots then distribute the detox proteins in the soil. For example, transgenic yellow poplar trees can thrive in mercury-tainted soil if they have a bacterial gene that encodes an enzyme, mercuric reductase, that converts a highly toxic form of mercury in soil to a less toxic gas. The tree's leaves then release the gas.

Bioremediation cleans up munitions dumps from wars. One application uses bacteria that normally break down trinitrotoluene—better known as TNT, the major ingredient in dynamite and

land mines. The enzyme that provides this capability is linked to the GFP gene. When the bacteria are spread in a contaminated area, they glow near land mines, revealing the locations much more specifically than a metal detector could. Once the land mines are removed, the bacteria die as their food vanishes.

### Key Concepts

1. In recombinant DNA technology, a cell receives a cloning vector that contains foreign DNA encoding a protein of interest. The universality of the genetic code and of restriction enzyme cutting sites make recombinant DNA technology possible.
2. Genes can be isolated from genomic DNA libraries or cDNA libraries.
3. Antibiotic resistance genes and gene variants that change the color of growth media are used to select cells bearing recombinant plasmids.
4. Recombinant DNA technology is used to manufacture large amounts of a pure protein in single cells and to create multicellular transgenic organisms.
5. Some transgenic plants use *Ti* plasmids to obtain foreign DNA. Transgenic animals receive foreign DNA naked, in liposomes, or by electroporation, microinjection, or particle bombardment. The gene must be transcribed and translated and its product collected and purified. For multicellular organisms, crosses may be necessary to obtain homozygous recessives.
6. Bioremediation uses natural abilities to detoxify environmental contaminants.

## 19.4 Monitoring Gene Function

DNA microarrays—or “gene chips”—are devices that reveal which genes are active and which are inactive in a tissue sample by looking at the mRNAs in a cell. They are also used to identify the genes themselves that are present in every cell of an organism. The creativity of the technique lies in choosing the samples and deciding which genes to consider. Chapter 1 introduced these two major uses of DNA microarrays: **gene expression profiling** that indicates which

genes are transcribed, and **DNA variation screening**, which detects mutations or SNPs (single nucleotide polymorphisms).

### Tracking the Aftermath of Spinal Cord Injury

Evaluating a spinal cord injury illustrates the basic steps in creating a DNA microarray to assess gene expression. Researchers knew that in the hours after such a devastating injury, immune system cells and inflammatory biochemicals flood the injured area, but it took gene expression profiling to reveal just how fast healing begins.

A microarray is a piece of glass or plastic that is about 1.5 centimeters square—smaller than a postage stamp. Many small pieces of DNA (oligonucleotides) of known sequence are attached to one surface, in a grid pattern. The researcher records the position of each DNA piece in the grid. In many applications, a sample from an abnormal situation (such as disease, injury, or environmental exposure) is compared to a normal control. **Figure 19.9** compares cerebrospinal fluid (CSF; the liquid that bathes the spinal cord) from an injured person (sample A) to fluid from a healthy person (sample B). Messenger RNAs are extracted from the samples and cDNAs made (see figure 19.6). The cDNAs from the injury sample are labeled with a red fluorescent dye, and the cDNAs from the control sample are labeled with a green fluorescent dye. These labeled DNAs are then applied to the microarray, which displays thousands of genes likely to be involved in a spinal cord injury. Increasingly researchers are probing microarrays studded with an entire human genome. This allows for surprises, avoiding the assumption that we know what to look for.

DNA that binds to complementary sequences on the grid fluoresce in place. A laser scanner then detects and converts the results to a colored image. Each position on the microarray can bind DNA pieces from both samples, either, or neither. The scanner also detects fluorescence intensities, which provides information on how strongly the gene is expressed. Then a computer interprets the pattern of gene expression, which may or may not make visual sense to the researcher—microarray experiments often yield surprise results.

For the spinal cord example, the visual data mean the following:

- Red indicates a gene expressed in CSF only when the spinal cord is injured (and presumably leaking inflammatory molecules).
- Green indicates a gene expressed in CSF only when the spinal cord is intact.
- Yellow indicates positions where both red- and green-bound dyes fluoresce, representing genes that are expressed whether or not the spinal cord has been injured.
- Black, or a lack of fluorescence, corresponds to DNA sequences that are not expressed in CSF.

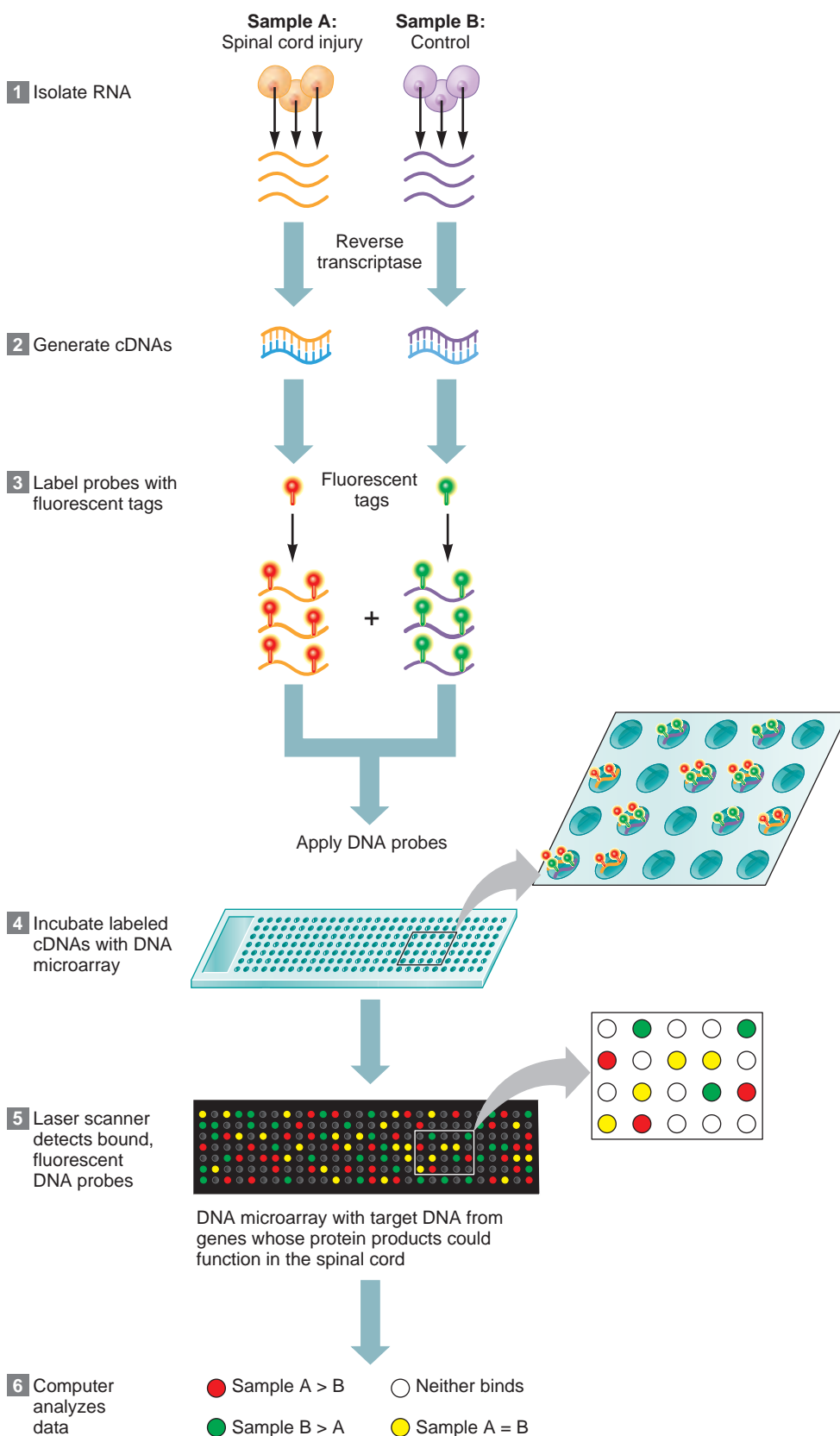
A computer analyzes the color and intensity pattern, which provides a snapshot of gene expression following spinal cord injury. The technique is even more powerful when repeated at different times after injury. When researchers did exactly that on injured rats, they discovered genes expressed just after the injury whose participation they never suspected. Their microarrays, summarized in **table 19.7**, revealed waves of expression of genes

Table 19.7

#### Gene Expression Profiling Chronicles Repair After Spinal Cord Injury

Time After Injury (rats)	Type of Increased Gene Expression
Day 1	Protective genes to preserve remaining tissue
Day 3	Growth, repair, cell division
Day 10	Repair of connective tissues
	Angiogenesis
Days 30–90	Blood vessels mature
	New type of connective tissue associated with healing





**Figure 19.9** A DNA microarray experiment reveals gene expression in response to spinal cord injury.

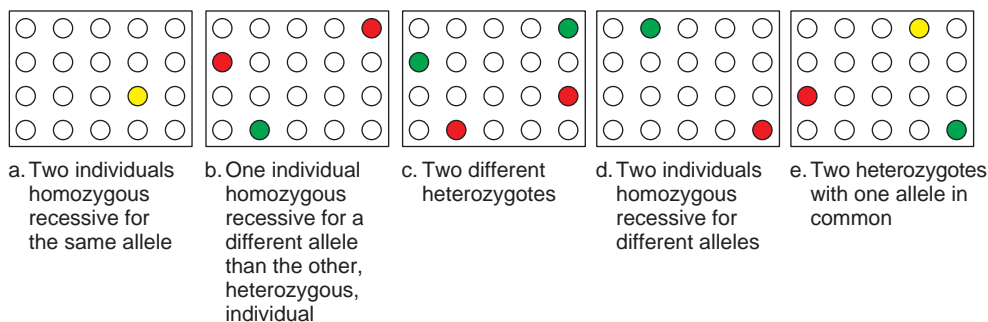
involved in healing. Analysis on the first day indicated activation of the same suite of genes whose protein products heal injury to the deep layer of skin—a total surprise that suggests new points for drugs to intervene.

### Solving a Problem: Interpreting a DNA Sequence Variation Microarray

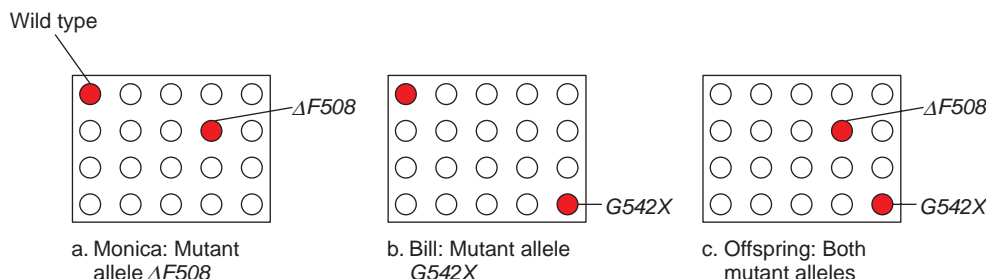
The second major type of DNA microarray experiment, a DNA sequence variation analysis, screens mutations, SNPs, and the wild type sequence for a particular gene. **Figure 19.10** shows possible patterns for comparing two individuals for a single-gene recessive disorder. Each person's microarray would have two fluorescing spots if he or she is a heterozygote (because there are two different alleles), or just one if he or she is a homozygote.

Interpreting the results of a DNA sequence variation analysis depends upon the specific nature of a disorder. In cystic fibrosis (CF), for example, a person could be homozygous recessive for a mutant allele that confers symptoms so mild that they had been attributed to recurrent respiratory infection. In another scenario, different alleles from two heterozygotes combine to cause severe illness in a child. This is what happened to Monica and Bill in **figure 9.11**. Routine screening during Monica's pregnancy revealed that she carries the common CF allele  $\Delta F508$ , which is associated with severe disease. Bill was then tested and found to be a carrier, too, but for the rarer allele  $G542X$ . Monica had amniocentesis, and a DNA microarray test of the sampled fetal cells revealed the pattern in **figure 19.11c**—both mutant alleles. The computer then consulted a database of known allele combinations and predicted a poor prognosis.

DNA sequence variation analysis also uses "SNP chips" that cover selected regions of more than one gene and can identify disease-associated variations over wide swaths of a genome. Such tests might predict whether variants in genes other than the one that causes CF could affect the phenotype of Monica and Bill's child, such



**Figure 19.10 DNA sequence variation analysis reveals alleles.** Heterozygotes have two fluorescent spots, and homozygotes have one. Target DNAs that bind two differently labeled DNAs fluoresce yellow.



**Figure 19.11 Microarrays show inheritance of cystic fibrosis.** Bill and Monica's child was unfortunate enough to receive rare CF alleles from both heterozygous parents.

## Key Concepts

1. DNA microarrays enable researchers to track gene expression and DNA variants.
2. In a DNA microarray experiment, DNA pieces of known sequence are attached to a glass or plastic chip, and differentially labeled sample cDNAs are applied.
3. The patterns and color intensities of spots indicate which genes are expressed or gene variants present. A laser scanner and computer recording interpret the results.

# Summary

## 19.1 Patenting DNA

1. **Biotechnology** alters cells or biochemicals to provide a product. It includes extracting natural products, altering an organism's genetic material, and combining DNA from different species.
2. A **transgenic** organism has DNA from a different species. **Recombinant DNA** comes from more than one type of organism. Both are possible because of the universality of the genetic code.
3. Patented DNA must be useful, novel, and non-obvious.

## 19.2 Amplifying DNA

4. Nucleic acid amplification, such as **PCR**, uses the power and specificity of DNA replication enzymes to selectively mass-produce DNA sequences.
5. In PCR, primers corresponding to a DNA sequence of interest direct polymerization of supplied nucleotides to make many copies.

## 19.3 Modifying DNA

6. **Recombinant DNA technology** is used to mass-produce proteins in bacteria or other single cells. Begun hesitantly in 1975, the technology has matured into a valuable method to produce proteins.
7. Constructing a recombinant DNA molecule begins when **restriction enzymes** cut both the gene of interest and a **cloning vector** at a short palindromic sequence, creating complementary "sticky ends." The cut foreign DNA and vector DNA are mixed, and vectors that pick up foreign DNA are selected.
8. **Genomic libraries** consist of recombinant cells containing fragments of a foreign genome. **DNA probes** are used to select genes of interest from genomic libraries. DNA probes may be synthetic, taken from another species, or a **cDNA**, which is reverse transcribed from mRNA.
9. Genes conferring antibiotic resistance and color changes in growth media are used to

select cells harboring recombinant DNA. Useful proteins are isolated and purified.

10. To produce a multicellular transgenic organism, a gamete in an animal or plant, somatic plant cell, or early embryo cell receives a foreign gene via a *Ti* plasmid (some plants) or other technique. The organism develops, including the change in each cell and passing it to the next generation. Heterozygotes for the transgene are then bred to yield homozygotes.
11. Recombinant DNA technology provides novel drugs, textiles, foods, and bioremediation.

## 19.4 Monitoring Gene Function

12. **DNA microarrays** are devices that hold DNA pieces to which fluorescently labeled DNA probes from samples are applied.
13. DNA microarrays are used in **gene expression profiling** and **DNA variation screening**.

# Review Questions

1. Cite three examples of a DNA sequence that meets requirements for patentability.
2. How are PCR and recombinant DNA technology similar, and how do they differ?
3. Describe the roles of each of the following tools in a biotechnology:
  - a. restriction enzymes
  - b. cloning vectors
  - c. DNA microarrays
4. How are cells containing recombinant DNA selected?
5. List the components of an experiment to produce recombinant human insulin in *E. coli* cells.
6. Why would recombinant DNA technology be restricted if the genetic code were not universal?
7. What is an advantage of a drug produced using recombinant DNA technology compared to one extracted from natural sources?
8. Describe three ways to insert foreign DNA into cells.
9. What is the difference between the types of information obtained in a gene expression profile and a DNA sequence variation analysis?
10. How does the information from a DNA microarray differ from the information in the haplotype of figure 5.17?

# Applied Questions

1. Phosphorus in pig excrement pollutes aquatic ecosystems, causing fish kills and algal blooms, and contributes to the greenhouse effect. *E. coli* produces an enzyme that breaks down phosphorus. Describe the steps to create a transgenic pig that secretes the bacterial enzyme, and therefore excretes less polluting poop.
2. To diagnose a rare form of encephalitis (brain inflammation), a researcher needs a million copies of a viral gene. She decides to use PCR on a sample of the patient's cerebrospinal fluid. If one cycle takes two minutes, how long will it take to obtain a millionfold amplification?
3. HIV infection was formerly diagnosed by detecting antibodies in a person's blood or documenting a decline in the number of the type of white blood cells that HIV initially infects. Why is PCR detection of HIV more sensitive?
4. Genetic modification endows organisms with novel abilities. From the following three lists (choose one item from each list), devise an experiment to produce a particular protein, and suggest its use.
  - a. Collagen is a connective tissue protein that is used in skincare products, shampoo, desserts, and in artificial skin. For many years it was obtained from the hooves and hides of cows collected from slaughterhouses. Human collagen can be manufactured in transgenic mice. Describe the advantages of the mouse system for obtaining collagen.
  - b. A woman was outraged to read a magazine article about certain genetic modification experiments. She wrote to this author, "Scientists have produced mice with human brains, mice with human blood flowing through their veins, and pigs with human cell surfaces. I am a big Mickey Mouse fan, but this is too much!" She is referring to:
    - Mice with spinal cord injuries that receive implants of human neural stem cells. They regain mobility.
    - Mice with human beta globin genes that are models of sickle cell disease.
    - Pigs that have some human proteins on their cell surfaces in attempts to make their organs more compatible for transplantation to humans.
  - c. Many people are alarmed at genetic modification experiments. What is your opinion about the utility and bioethics of each of these examples of genetic modification? (The first example is actually a cell implant, not genetic modification. But the principle of mixing material from two species is similar.)
5. c. There was no public outcry over the development of human insulin produced in bacterial cells and used to treat diabetes. Yet some people object to mixing DNA from different species in agricultural biotechnology. Why do you think that the same general technique is perceived as beneficial in one situation, yet a threat in another?
6. A human oncogene called *ras* is inserted into mice, creating transgenic animals that develop a variety of tumors. Why are mouse cells able to transcribe and translate human genes?
7. In a DNA microarray experiment, the researcher selects the DNA pieces that are attached to the grid. For example, to study an injury, he or she might choose genes known to be involved in the inflammatory response. How might this approach be limited?
8. Devise an experiment using DNA microarrays to determine whether men and women have different hormonal responses to watching an emotional film. (A hormone is a type of messenger molecule that is carried in the blood).

Organism	Biological Fluid	Protein Product
pig	milk	human beta globin chains
cow	semen	human collagen
goat	silk	human EPO
chicken	egg white	human tPA
aspen tree	sap	human interferon
silkworm	blood plasma	jellyfish GFP
rabbit	honey	human clotting factor
mouse	saliva	alpha-1-antitrypsin

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 19**, and **Web Activities** to find the website links needed to complete the following activities.

10. Use the Web to identify three drugs made using recombinant DNA technology, and list the conditions they are used to treat. (Check websites for the following companies: Genzyme, Amgen, Biomarin Pharmaceuticals, Genentech, Serono, and Eli Lilly.)

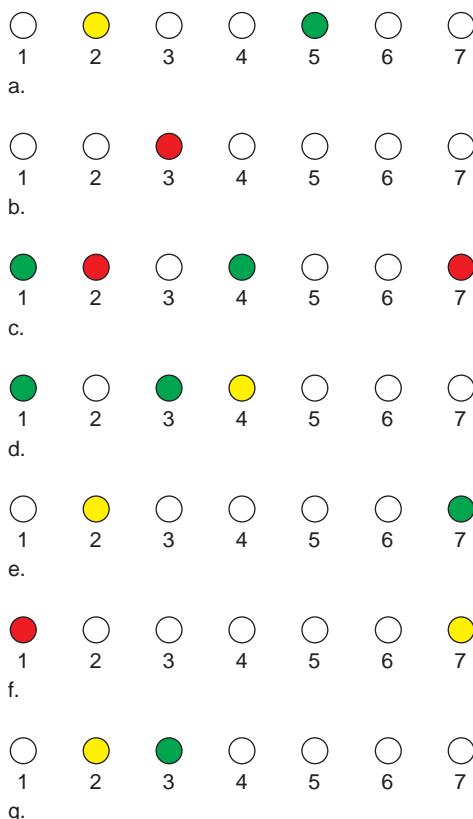


11. About how many DNA patents are currently being evaluated at the U.S. Patent and Trademark office, and what percentage of them are for DNA from the human genome?

### Case Studies

12. In the 1990s, Australian researcher Malcolm Simons filed patents on the use of non-protein-encoding parts of the human genome to predict the risk of developing certain diseases. At the time, research interest focused on the protein-encoding parts of the genome—some people called the rest “junk.” But toward the turn of the century, research correlating SNP patterns in the “junk” to disease risk became a top priority at many biotech companies, and researchers there encountered Simons’s patents. He is now asking researchers to pay to use his idea. Many geneticists denounced Simons’s actions as counter to the spirit of open access to human genome information. Do you support or object to Simons’s restricting access to the DNA sequences he predicted would have clinical utility?
13. Nancy is a transgenic sheep who produces human alpha-1-antitrypsin (AAT) in her milk. This protein, normally found in blood serum, enables the microscopic air sacs in the lungs to inflate. Without it, inherited emphysema results. Donated blood cannot yield enough AAT to help the thousands of people who need it. Describe the steps taken to enable Nancy to secrete human AAT in her milk.
14. To investigate causes of acne, researchers used DNA microarrays that cover the

entire human genome. Samples came from facial skin of people with flawless complexions and from people with severe acne. In the following simplified portion of a DNA microarray, one sample is labeled green and comes from healthy skin; a second sample is labeled red and represents skin with acne. Sites on the microarray where both probes bind fluoresce yellow. The genes are indicated by letter and number.



- a. Which genes are expressed in skin whether or not a person has acne?
- b. Which genes are expressed only when acne develops?
- c. List three DNA pieces that correspond to genes that are not expressed in skin.
- d. How would you use microarrays to trace changes in gene expression as acne begins and worsens?
- e. Design a microarray experiment to explore gene expression in response to sunburn.

## A Second Look

- Do you think that cheese that has been made using an enzyme from a genetically modified organism is more dangerous than eating cheese made using an enzyme from another source? Cite a reason for your answer.
- Why do you think that there has been no public outcry about cheese made using

an enzyme from a genetically modified organism?

- What can a vegetarian who likes cheese do who is opposed to genetic modification?

Learn to apply the skills of a genetic counselor with additional cases found in the *Case Workbook of Human Genetics*.

Hemophilia A and B  
Infertility drugs  
Transgenic tobacco



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.



# Genetic Testing and Treatment

## CHAPTER CONTENTS

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## GENE THERAPY FOR CANAVAN DISEASE

Ilyce and Mike Randell, of Buffalo Grove, Illinois, were worried. Their 5-month-old son, Max, born in October, 1997, could not hold up his head, roll over, reach for objects, or sleep more than an hour, and he was unresponsive. When doctors diagnosed Canavan disease (OMIM 271900), which robs brain neurons of their fatty sheaths so that the brain slowly degenerates, they suggested that the best place for the golden-haired boy would be a nursing home, to live out his expected two years. Instead, Max became the youngest person to receive gene therapy for a degenerative brain disease. Today he plays with brother Alex, attends school, and gets around in a wheelchair. He communicates by using a computer and an eyetracking system originally developed by market researchers to learn what people look at when watching TV ads. His greatest joy is horseback riding, which he has done, with help, since he was 5 years old.

Max received his first gene therapy, to test safety, in 1998, and then a more intensive version in 2001. Ninety billion viral particles that each carried a corrected copy of the gene were delivered through six holes drilled into his skull. Although his progress is slight—his head and neck are stronger, he sees better, and he has more control over his limbs—he may be paving the way for delivery of healing genes for common brain disorders, such as Parkinson disease and Alzheimer disease. Only about 4,000 children in the world have Canavan disease, and lifespan is 10 years.

The news most often mentions gene therapy failures. But Ilyce Randell tells Max's tale whenever a reporter asks. "I cannot even begin to describe the joy we feel just seeing him regain even the slightest bit of functional mobility; he just beams with pride when his body does what he wants it to. None of this would have been possible for Max if he had not received gene therapy."



Max Randell's experience has been a gene therapy success story.



20.1 Genetic Counseling

Genetic disease strikes families in a way that other conditions do not, because members are affected with predictable frequencies. Living with genetic disease typically takes several steps:

- Realizing something is wrong
- Diagnosing the condition and understanding its course
- Identifying a mutation in others
- Treating symptoms

Genetic counselors are health care professionals who help individuals and families along this journey.

Until recently, most health care professionals received limited training in genetics. Since the 1970s, genetic counselors have led the way in explaining single-gene disease inheritance patterns and recurrence risks to patients. Today, their role is expanding to embrace multifactorial disorders, such as cancer and cardiovascular disease.

The knowledge that genetic counselors share with their patients reflects what you have read so far in this book, presented in a personalized manner and applied to a specific disorder. A genetic counselor might explain Mendel’s laws, but substitute the particular family’s situation for the pea plant experiments.

A genetic counseling session begins with a discussion of the family’s health history. Using a computer program or pencil and paper, the counselor derives a pedigree, then explains the risks of recurrence

for particular family members for their particular inherited illness (figure 20.1). Sometimes she will present possibilities and defer discussion of specific risks until test results are available. Table 20.1

Reasons to seek genetic counseling:

- Family history of abnormal chromosomes
- Elevated risk of single gene disorder
- Family history of multifactorial disorder
- Family history of cancer



Genetic counseling sessions:

- Family history
- Pedigree construction
- Information provided on specific disorders, modes of inheritance, tests to identify at-risk family members
- Testing arranged, discussion of results
- Links to support groups, appropriate services
- Follow-up contact



Figure 20.1 The genetic counseling process.

Table 20.1  
Down Syndrome Scenarios

Couple	Risks	Tests
1. Christy and Eric are 24 years old and have no children, with no family history of reproductive problems or genetic disease.	Risk of trisomy 21 Down syndrome based on maternal age is 1 in 1,250.	A physician using older statistics for amniocentesis causing miscarriage (1 in 300) would recommend maternal serum screening only. A physician using more recent risk estimate (1 in 1,600) would advise amnio.
2. Effie and Randy have a child with trisomy 21 Down syndrome.	Empiric risk of recurrence for aneuploidy is 1 in 100.	CVS or amnio
3. Tanisha and Dillon have had spontaneous abortion, stillbirth, birth defects, and their son has Down syndrome. Dillon is a translocation carrier.	Risk of Down syndrome 1 in 6; risk of spontaneous abortion 1 in 2 (see figure 13.19)	CVS or amnio
4. Neela and Ray have no children, have no family history of reproductive or genetic problems, and are each 48 years old.	Risk of trisomy 21 Down syndrome for maternal age 48 is 1 in 14	CVS or amnio

CVS = Chorionic villus sampling  
amnio = amniocentesis

illustrates different testing possibilities and risks for several couples concerned with the same condition—Down syndrome, which can arise in several ways. The counselor will also explain which second degree relatives—aunts, uncles, and cousins—might benefit from being informed about a diagnosis.

The counselor provides detailed information on the condition and refers the family to support groups. If a couple wants to have a biological child who does not have the illness, a discussion of assisted reproductive technologies (see chapter 21) might be in order.

A large part of the genetic counselor's job is to determine when specific biochemical, gene, or chromosome tests are appropriate, and to arrange for people to take the tests. The counselor then interprets test results and helps the patient or family choose among medical options. Genetic counselors are also often asked to provide information on drugs that can cause birth defects, although this really is related to development, not genetics. People seek genetic counseling for either of two general reasons: prenatal diagnosis, and a disease in the family.

Prenatal genetic counseling typically presents population (empiric) and family-based risks, explains tests, and discusses whether the benefits of testing outweigh the risks. The couple or woman decide whether amniocentesis, chorionic villus sampling, maternal serum screening, or no testing is appropriate for them. Part of a prenatal genetic counseling session is to explain that tests that rule out some conditions do not guarantee a healthy baby. For example, many people assume that amniocentesis checks every gene, when it actually detects only large-scale chromosome aberrations. Single-gene tests must be requested separately. If a test reveals that the fetus has a serious medical condition, the counselor discusses possible outcomes, treatment plans, and the option of ending the pregnancy.

Counseling when there is an inherited disease in a family is another matter. For recessive disorders, the affected individual is usually a child, such as Max and Canavan disease, discussed in the chapter opener. Illness in the first affected child is often a surprise, and especially if this is a first child, recognition of a problem may take months. Some single-gene disorders are so rare that

finding a doctor who recognizes symptoms and realizes what to test for can also delay diagnosis, as a mother explains in the *In Your Own Words* essay in chapter 12 for her daughter with familial dysautonomia.

Often the hardest information to communicate is the risk to subsequent children. Many people think that if one child is affected with an autosomal recessive condition, then the next three will be healthy, rather than realizing that each offspring has a 1 in 4 chance of inheriting the illness. Counseling for subsequent pregnancies requires great sensitivity and sometimes a little bit of mind reading. Many people will not terminate a pregnancy when the fetus has a condition that already affects their living child, yet some will see that as the kindest option. Genetic counselors must respect these feelings, and tailor the options discussed accordingly.

Counseling for adult-onset disorders does not have the problem of potential parents making life-or-death decisions for existing or future children, but presents the conflicting feelings of people choosing whether or not to find out if a disease is likely in their future. Often, they have seen loved ones suffer with the illness. This is the case for Huntington disease (see Bioethics: Choices for the Future on page 77). Predictive tests are introducing a new type of patient, the “genetically unwell”—those with mutant genes but no symptoms (yet).

So far studies are finding that most healthy people offered such tests decline them. A counselor can direct patients to these studies. As of now, a “diagnosis” is still based on identifying symptoms. A disease-associated genotype indicates elevated risk, not a medical diagnosis. It is a little like detecting high cholesterol in a healthy person.

When the field of genetic counseling was founded in the 1970s, it was “nondirective,” meaning that the practitioner did not offer an opinion or suggest a course of action, but only presented options. That approach is changing as the field moves from analyzing hard-to-treat, rare single-gene disorders to considering inherited susceptibilities to more common illnesses that are more treatable, and for which lifestyle changes might realistically alter outcome. A more recent definition of the role of the genetic counselor is “shared deliberation and decision making between the counselor and the client.”

In some cases it can be challenging to provide nondirective counseling. One such situation is when a couple has the same autosomal recessive form of blindness or deafness, but want to have children, even though they know that the children will be blind or deaf, because they, too, will be homozygous recessive. In one case, when a genetic counselor suggested adoption or intrauterine insemination by donor, the couple considered the advice a value judgment on their choice to have a child.

The United States has about 3,000 genetic counselors. They work in medical centers, clinics, hospitals, biotechnology companies, pharmaceutical companies, research and diagnostic testing laboratories, and medical practices. Because there are so few genetic counselors, and most of them practice in urban areas, access to their services is limited. Finding a genetic counselor with a specific expertise is difficult. For example, only 400 genetic counselors in the United States are specially trained in cancer genetic counseling. Due to the shortage of counselors and demand for their services, sometimes other types of health care professionals, such as physicians, nurses, social workers, and PhD geneticists, provide counseling. One survey found that dietitians, physical therapists, psychologists, and speech-language pathologists regularly discuss genetics with their patients, who regularly ask questions about heredity.

Other stand-ins for trained genetic counselors can be less effective. For example, some companies that provide genetic tests for cancer risk train licensed practical nurses to counsel patients, or use “virtual” genetic counseling, in which an interactive computer program calculates risks and provides basic information. In one study, women seeking genetic counseling for possibly carrying either the *BRCA1* or *BRCA2* genes that cause breast cancer had virtual counseling. Although the experience increased knowledge, especially for low-risk women who had overestimated their danger, it did not lower anxiety nearly as well as a real genetic counselor with expertise in cancer genetics and psychology.

Other medical professionals sometimes lack the unique combination of skills that a genetic counselor offers. For example, a survey of mothers of children with trisomy

21 Down syndrome found many instances of physicians without appropriate training in psychology presenting only negative facts to new parents. Said one mother, “The doctor flat out told my husband that this could have been prevented or discontinued at an earlier stage of the pregnancy.” Another woman overheard her doctor call her son an “FLK,” which is medical slang for “funny-looking kid.”

As genetic testing becomes more common as we learn more about the human genome, the need will increase for genetic counselors, or other genetics-savvy professionals, to help families best use the new information.

### Key Concepts

1. A genetic counselor provides information to individuals, couples expecting children, and families about modes of inheritance, recurrence risks, genetic tests, and treatments.
2. The counselor helps people make decisions while being sensitive to individual choices.
3. The shortage of genetic counselors has led other health care professionals to provide the service, and has resulted in the use of computer programs to dispense information and advice.

## 20.2 Genetic Testing

Genetic testing is increasingly becoming part of health care. The field was founded on tests for newborns, many of which are now mandated by law, but today also includes direct-to-consumer tests available on the web to anyone who can afford them. While genetic testing can suggest ways that people can live more healthy lifestyles, and in some cases refine diagnoses and thereby allow more tailored treatments, it also raises issues of risk and privacy.

### Newborn Screening

If Max Randell had been born today, newborn screening tests would have likely detected the mutant genes that caused his Canavan disease. Such newborn screening is one example of the growing incorporation of genetic testing into health care. Some of the tests and technologies aren’t actually new, but what is new is the scope, and the economic and ethical issues that arise with genetic testing at the population level.

Technology to detect and treat inborn errors of metabolism started with phenylketonuria (PKU). Beginning in 1961, the Guthrie test sampled blood from a newborn’s heel and tested for the amino acid buildup that indicates PKU, discussed in section 5.1.

In 1963, a specialized diet (legally termed a “medical food” so that insurance will cover the high cost) became available, with dramatic positive results. Today, a technique called tandem mass spectrometry is used to identify the chemical imbalances of many inborn errors on one blood sample. Then the polymerase chain reaction (see figure 19.2) amplifies specific mutations so that they can be identified.

Increasing use of tandem mass spectrometry to simultaneously detect many inborn errors of metabolism is widening the availability of tests for certain rare conditions. For many years, in the United States, the March of Dimes recommended such newborn screening for the eight conditions listed in table 20.2, plus congenital hearing loss. States could provide whatever number of tests they liked, which meant that a child with a certain disorder could be diagnosed and possibly treated in one state, but not in another. In 2005, following recommendations of the American College of Medical Genetics, the U.S. government’s Maternal and Child Health Bureau mandated testing for 29 conditions that are treatable and recommended testing for an additional 25 conditions that are currently not treatable. Testing for untreatable conditions can help a physician narrow down a diagnosis by ruling out possibilities.

Table 20.2

Newborn Screening Tests

Disease	Incidence	Symptoms	Treatment
Biotinidase deficiency	1/70,000 Rare in blacks or Asians	Convulsions; hair, hearing, and vision loss; developmental abnormalities, coma, sometimes death	Most physical symptoms reversed by oral biotin
Maple syrup urine disease	1/250,000–300,000 More common in blacks and Asians	Lethargy, mental retardation, sweet-smelling urine, irritability, vomiting, coma, death by one month	Diet very low in overproduced amino acids
Congenital adrenal hyperplasia	1/12,000 whites, 1/15,000 Jews, 1/680 Yupik eskimos	Masculinized female genitalia, dehydration, precocious puberty in males, accelerated growth, short stature, ambiguous sexual characteristics	Hormone replacement, surgery
Congenital hypothyroidism	1/3,600–5,000 whites; rare in blacks, more common in Hispanics	Mental retardation, growth failure, hearing loss, underactive thyroid, neurological impairment	Hormone replacement
Galactosemia	1/60,000–80,000	Muscle weakness, cerebral palsy, seizures, mental retardation, cataracts, liver disease	Galactose-free diet
Homocystinuria	1/50,000–150,000	Blood clots, thin bones, mental retardation, seizures, muscle weakness, mental disturbances	Low-methionine, high-cysteine diet, drugs
Phenylketonuria (PKU)	1/10,000–25,000	Mental retardation	Low-phenylalanine diet
Sickle cell and other hemoglobinopathies	1/400 U.S. blacks	Joint pain, severe infection, leg ulcers, developmental delay	Prophylactic antibiotics



Selecting which disorders to test for illustrates the ethical and economic issues of newborn testing. The advantage of early detection is clear for a treatable condition, such as PKU or maple syrup urine disease, described in Reading 2.1—preventing symptoms and enabling normal development. But what might be the consequences of revealing a serious disorder without the ability to prevent symptoms or halt the disease’s progression? Could testing cause more harm than good?

Even though inborn errors of metabolism are very rare, testing for them is not costly, because a battery of tests requires only one blood sample, which is routinely taken anyway. Screening for 50 conditions using tandem mass spectrometry costs less than the price of a pair of running shoes. Yet the economics can be viewed another way, by considering population statistics. Each year in the United States, 4 million babies are born, and 0.1 percent of them have one of the 54 disorders that are most commonly detected with newborn screening. Health officials in some states argue that the cost of testing so many to detect so few is not practical. Supporters of testing counter that the costs saved by being able to treat identified children justifies the expense of populationwide testing.

Newborns are not the only individuals offered genetic testing, and not all genetic tests are for disorders as rare as those detected in newborns. Section 13.2 describes several tests and techniques that provide clues to the genetic health of a fetus. Throughout life, genetic tests may help to confirm or exclude a diagnosis based on symptoms. Chapter 18 discusses how gene expression profiling is impacting the diagnosis and treatment of cancer. Many genetic tests are also being used to predict elevated risks and inherited susceptibilities to a variety of illnesses. In the future, such tests will increasingly provide information on environmental factors that pose a health threat to individuals with particular genetic backgrounds. **Table 20.3** summarizes some uses of genetic tests.

### Direct-To-Consumer Genetic Testing

Many companies offer genetic tests on their websites. A customer sends in a DNA sample on a cheek swab, and for anywhere from \$200 to \$2,000, learns which alleles he or she has for particular selected genes. **Table 20.4** lists some of them. While the genes and tests are real, and the websites generally list real scientific papers describing the genes, this information is usually population-based. What’s missing is how the findings predict

or describe a particular individual’s health. A gene variant that tracks with heart disease in a large study of Swedish women, for example, may not apply to an Asian man taking a test. Without appropriate counseling by a health care professional—not a voice over the phone or a FAQ list on a website—customers can suffer undue stress or even make decisions based on partial information that can endanger health. Companies may offer to send detailed reports to the customer’s physician, but this may compromise privacy—a reason that many people use direct-to-consumer tests.

A disease that illustrates potential problems with direct-to-consumer tests is hereditary hemochromatosis (HH). HH is an “iron overload” disease. Cells in the small intestine absorb too much iron from food. Over many years, the excess iron is deposited throughout the body, causing various symptoms and secondary conditions. The liver develops cirrhosis (scarring) and sometimes cancer; the heart may fail or beat irregularly; an iron-loaded pancreas may cause diabetes; joints become arthritic; and the skin darkens. Early signs and symptoms include chronic fatigue, infection, hair loss, infertility, muscle pain, and feeling cold. More men than women develop HH symptoms, because a woman loses some blood each month when she

**Table 20.3**  
Types of Genetic Tests

Type of Test	Information Provided	Example
Carrier screen	Identifies heterozygotes—people with one copy of a mutant gene	The healthy sibling of a child with CF is tested—chance of being a carrier is 2/3.
Prenatal test	Detects mutant allele in a fetus for a condition present in a family	A couple who know they are carriers of Tay-Sachs disease has a fetus tested.
Prenatal screen	Tests embryos or fetuses from a population for increased risk of a condition, not based on family history	A pregnant woman’s blood is tested for elevated level of a protein indicating increased risk for a neural tube defect.
Newborn screen	Populationwide testing for several treatable inborn errors of metabolism	A child with identified sickle cell disease genes at birth can ease or delay symptoms with antibiotics.
Diagnostic test	Confirms diagnosis based on symptoms	A child with “failure to thrive” and frequent lung infections is tested for mutant alleles for CF.
Predisposition test	Detects allele(s) associated with an illness, but not absolutely diagnostic of it	A young Jewish woman with a strong family history of breast cancer has a mutant <i>BRCA1</i> allele, giving her an 85 percent lifetime risk of developing the condition.
Predictive test	Detects highly penetrant mutation with adult onset in an individual at high risk based on family history	A healthy person is tested for the Huntington disease mutation because a parent has the condition.

Table 20.4

## Some Direct-to-Consumer Gene Tests

Indication	OMIM	Function
Cardiovascular health		
MTHFR (methylene tetrahydrofolate reductase)	607093	Folic acid and homocysteine metabolism
MnSOD (manganese superoxide dismutase)	147460	Anti-oxidant
IL-6 (interleukin-6)	147620	Inflammatory response
CETP (cholesteryl ester transfer protein)	118470	Cholesterol metabolism
ACE (angiotensin 1-converting enzyme)	106180	Controls blood pressure
Diabetes		
PPAR gamma (peroxisome proliferator-activated receptor-gamma)	604517	Controls fat cell differentiation
TNF-alpha (tumor necrosis factor alpha)	191160	Insulin resistance (ability of cells to admit insulin)
Osteoporosis		
VDR (vitamin D receptor)	601769	Regulates bone mineral density
COL1A1 (collagen type 1)	120150	Bone component

menstruates. For women past the age of menopause, the sex ratio equalizes.

In the United States, 1.5 million people have this autosomal recessive condition, and 32 million people—1 in 8—carry a mutant allele for the *HH* gene. It is most common among those of Irish, Scottish, or British descent. Diagnosis is important because of the severity of symptoms and because the body's iron levels are easily controllable—blood is removed every few months.

To diagnose HH, a blood test detects increase in ferritin, a protein that carries iron, and a liver biopsy confirms this finding. Determining the genotype alone is not sufficient for diagnosis because the penetrance is very low. That is, although most people with iron overload have mutations in the *HH* gene, only a small percentage of people with a homozygous recessive genotype actually have symptoms. Therefore, at-home testing for *HH* alleles could be confusing to consumers unfamiliar with the uncertainty of genetics.

Some direct-to-consumer testing companies offer genetic tests along with general questionnaires about diet, exer-

cise, and lifestyle habits. The company then sends a “nutrigenetics” profile with dietary suggestions—often with a pitch to purchase a pricy package of exactly the supplements that an individual supposedly needs to prevent his or her genetic fate.

After the media spread the word of these services, the U.S. government's Government Accountability Office tested the tests. An investigator took two DNA samples—one from a 9-month-old girl and the other from a 48-year-old man—and created 14 lifestyle/dietary profiles for these “fictitious consumers”—12 for the female, 2 for the male. The samples were sent to four companies that advertise nutrigenetics testing on the web. Here is an example of the information sent to the companies and the advice received:

- The DNA from the man was submitted as being from a 32-year-old male, 150 pounds, 5'9", who smokes, rarely exercises, drinks coffee and takes vitamin supplements.
- The DNA from the baby girl was submitted as a 33-year-old woman, 185

pounds, 5' 5", who smokes, drinks a lot of coffee, doesn't exercise, and eats a lot of dairy, grains, and fats.

- The same baby girl DNA was also submitted as a 59-year-old man, 140 pounds, 5' 7", who exercises, never smoked, takes vitamins, hates coffee, and eats a lot of protein and fried foods.

The elevated risks found for the three were exactly the same: osteoporosis, hypertension, type 2 diabetes, and heart disease. One company would provide the appropriate multivitamin supplements for \$1200, which the investigation found to be worth about \$35. Recommendations tended to state the obvious, such as advising a smoker to quit. The advice tracked with the fictional lifestyle/diet information, and not genetics. Concluded the study: “Although these recommendations may be beneficial to consumers in that they constitute common sense health and dietary guidance, DNA analysis is not needed to generate this advice.” Some of the suggestions could even be dangerous, such as vitamin excesses in people with certain medical conditions. (A health history was not required.)

## Genetic Privacy Revisited

Genetic testing provides information that can have effects beyond the individual. People are very concerned about who should have access to such information. Physicians must weigh the risks and benefits of keeping medical information confidential when to do so could harm others. Consider the following true cases:

- A couple suffered several miscarriages, then had a child with multiple problems. A chromosome check found that the father carried a translocation. The man's siblings may also have carried the translocated chromosome, but the couple did not want to tell anyone the test result.
- Mr. and Mrs. Gold knew that their mildly retarded son had a chromosomal deletion. A questionnaire from the special education department in their school district asked if he'd ever had a chromosome test. If the parents answered yes, their child may have been stigmatized. If they answered no, he may not have gotten appropriate support. They did not know what to do.

- A subway driver had familial hypercholesterolemia. Although he had chest pains and high blood pressure and serum cholesterol, he had never had a heart attack. He knew that he could suddenly die, but he wouldn't tell the transportation department because he was retiring in a few months. The genetic counselor knew the diagnosis.

These cases are from the 1980s and 1990s, before many genetic tests were available. Today, the question of genetic privacy is arising more and more with cancer susceptibility, because knowledge can warn a person to have specific medical tests or change lifestyle habits. For example, one physician did not know what to do when testing revealed that her patient had inherited a *BRCA1* mutation, but the patient refused to share the information with her sister, who has a 50 percent chance of having inherited it, too. To keep quiet denies the sister the chance of early detection; to tell her breaks the doctor's confidentiality with her patient. Did the doctor have a "duty to warn" the patient's sister?

Medical decision making on the "duty to warn" often refers to legal precedents, specifically a 1976 case, *Tarasoff versus the Regents of the University of California*. A psychiatrist did not warn a young woman that her parent, who was the patient, had threatened to kill her. The woman was indeed murdered, and the California Supreme Court

decided that the doctor should have warned the victim. Since then, several cases of "duty to warn" about genetic disease risks have gone through the courts (**table 20.5**).

During the Clinton administration, a presidential commission drew up guidelines for the "duty to warn" dilemma. According to this report, a physician should disclose information if

1. harm from keeping confidentiality outweighs the harm from breaching it.
2. relative(s) at risk can be identified.
3. failure to warn places the person at great risk of harm.

Medical organizations have had their say on the "duty to warn" situation too. The American Medical Association advises physicians to discuss with patients, before or at the time of genetic testing, the situations in which the doctor feels he or she should notify relatives. This discussion should be part of the informed consent process. Regulations are stricter in Canada, where physicians have a "duty to rescue" when breaking a confidence can help someone. In the United States, however, the idea of mandating "duty to warn" has met with much opposition. The National Alliance for Breast Cancer Organizations and other consumer groups have expressed concern that such a practice could discourage people from taking genetic tests, as well as

place too great a demand on physicians to counsel relatives of their patients. But from a legal standpoint, breaching confidentiality in the United States goes against the HIPAA (Health Insurance Portability and Accountability Act of 1996) regulation that maintains privacy of medical records.

Perhaps the solution to the duty-to-warn dilemma is to tackle this issue on a case-by-case basis, rather than using legal precedents that did not apply to genetic disease, or legislating new guidelines. The biological and psychological aspects of inherited disease or disease susceptibilities must be taken into account. These include the penetrance of a disease-causing mutation, the degree of susceptibility of a particular individual, and treatment availability. Health care professionals must also respect feelings of guilt about passing a health-related gene to children, not inheriting a condition when a sibling has, or surviving a condition when relatives do not.

### Key Concepts

1. Newborn screening is using tandem mass spectrometry to expand coverage to dozens of inborn errors of metabolism.
2. Genetic tests are becoming an increasing part of diagnostic medicine, for rare and common disorders.
3. Direct-to-consumer genetic testing can be dangerous if incomplete or too generalized results are given without appropriate counseling.
4. Medical organizations consider legal precedents as well as the specific circumstances of genetic testing to decide when to break a confidence concerning a test result.

**Table 20.5**  
Legal Cases on "Duty to Warn" of Cancer Risk

Case	Details
<i>Pate v. Threlkel</i> (1995)	Daughter sued doctor for not informing her that her mother had autosomal dominant medullary thyroid cancer, the most serious type. Heidi Pate was diagnosed three years after her mother; her case was advanced. Early detection has a higher chance of cure. The Supreme Court of Florida ruled in her favor.
<i>Safer v. Estate of Pack</i> (1996)	Daughter sued doctor for not informing family members when her father was diagnosed with colon cancer 30 years earlier that it is hereditary and occurs by age 40. By the time of the daughter's diagnosis, the disease was advanced. New Jersey Supreme Court ruled in doctor's favor because plaintiff had indeed been tested as a child, but her mother had not told her of the family history.
<i>Molloy v. Meier</i> (2004)	Mother sued physician for not informing her that fragile X syndrome, diagnosed 10 years earlier in her daughter, could affect half-siblings. Mother would not have had other children if she'd known. The court decided in the mother's favor in this "wrongful conception" suit.

### 20.3 Treating Genetic Disease

Development of genetic testing has raced past development of treatments for genetic disease. Treatment has evolved in three phases:

- replacing missing proteins with material from donors
- obtaining pure proteins using recombinant DNA technology
- **gene therapy**, which replaces mutant alleles



Table 20.6

## Enzyme Replacement Therapy

Disease	OMIM	Enzyme	Mode*	Symptoms
Fabry disease	301500	alpha galactosidase	xlr	Skin lesions, abdominal pain, heart problems, kidney failure, symptoms begin any time
Gaucher disease	230800	glucocerebrosidase	ar	Enlarged spleen, bone lesions, skin pigmentation, symptoms begin any time
Hunter disease (mucopolysaccharidosis I H/S)	309900	iduronate sulfatase	xlr	Dwarfism, abnormal facial features, enlarged liver and spleen, heart problems, deafness, urination of unusual metabolites, mild and severe forms
Hurler-Scheie disease (mucopolysaccharidosis II)	607015	alpha-L-iduronidase	ar	Short stature, corneal clouding, stiff joints, umbilical hernia, enlarged liver and spleen, mental retardation, onset at 3 to 8 years, survival to adulthood
Pompe disease	232300	acid alpha-glucosidase	ar	Heart problems, flaccid muscles; infantile, juvenile, and adult forms

\*xlr = X-linked recessive  
ar = autosomal recessive

Alleviating or even preventing symptoms of some genetic disorders is possible at the phenotypic and/or genotypic levels.

## Treating the Phenotype

Preventing a disease-associated phenotype can be as straightforward as supplying a missing protein. A child with cystic fibrosis sprinkles powdered digestive enzymes from cows onto applesauce, which she eats before each meal to replace the enzymes her clogged pancreas cannot secrete. A boy with hemophilia receives a clotting factor. Even wearing eyeglasses is a way of altering the expression of one's inheritance.

Several inborn errors of metabolism are treated with enzyme replacement therapy (**table 20.6**). An ongoing success story is Pompe disease, also known as glycogen storage disease type II. In this autosomal recessive inborn error, deficiency of one of the 40 types of enzymes found in the cell's lysosomes leads to buildup of the carbohydrate glycogen, which is chemically similar to starch. The buildup harms all three types of muscle cells—cardiac, smooth, and skeletal. The infantile form of the disease affects 1 in 40,000 live births in the United States overall, but 1 in 14,000 African Americans. Fewer than 10,000 people in the world have Pompe disease, and only 133 cases have been described in medical journals. Of those cases, the average age at death is 7 months, with only 8 percent surviving to

one year, and only 2 of the 133 living until 18 months of age.

Researchers began working on enzyme replacement therapy for Pompe disease in 1998, and were able to produce the human enzyme in transgenic rabbit milk and from recombinant hamster cells growing in culture. (Chapter 19 explains how recombinant DNA technology enables cells and transgenic organisms to produce therapeutic human proteins.) In an initial pilot study of 18 very ill babies, infusion of the hamster-derived enzyme led to 83 percent survival, without the need for a ventilator, at 18 months.

For a British family, enzyme replacement therapy had a dramatic effect (**figure 20.2**). Their first child died of Pompe disease before his sixth month. The earliest sign was “floppiness”—he couldn't hold up his head, and if his arm was lifted and released, it would flop down. When his breathing became difficult, his parents took him to the hospital, where doctors discovered an enlarged heart. Sampling of heart tissue revealed the glycogen buildup of Pompe disease, but there was no treatment. The family had two healthy sons, and then a daughter. When she couldn't hold her head up by three months and had difficulty eating, she was tested and found to have the disease. Her heart was five times normal size, yet with less than 10 percent normal function. The little girl was near death when she was admitted to the clinical trial for the enzyme replacement therapy, called Myozyme. She is now school age,

and although her legs remain weak, she gets around by scooting on her rear. Her speech is much-improved and her vocabulary growing, and she no longer has to be tube fed. She and 280 others eventually given the drug are surviving, but it is too soon to tell how successful the treatment will be in the long term. But for now, she is enjoying a childhood that she otherwise would not have had.

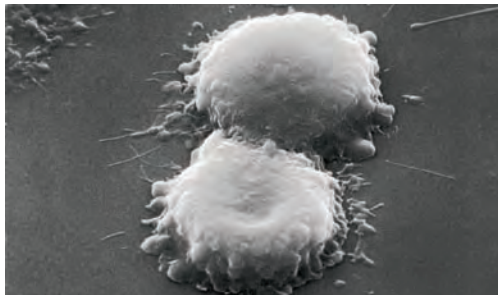
## Gene Therapy

More than a thousand clinical trials of gene therapies have been conducted since 1990. As the new millennium dawned, researchers had expected that the sequencing of the human genome would accelerate the pace of gene therapy development. Instead, new information about the complexity of how genes interact, and a few cases where the experimental treatment harmed the patient, have led to a reevaluation of the idea that we can augment or replace a gene with predictable effects.

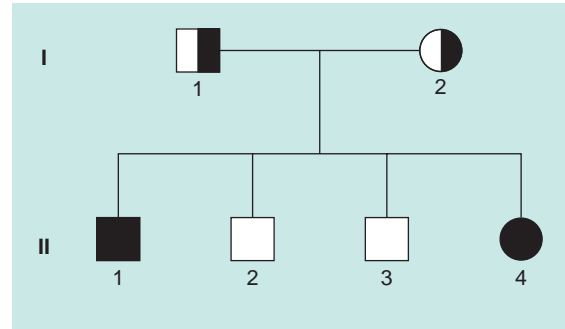
Altering genes to treat an inherited disorder theoretically can provide a longer-lasting effect than treating symptoms, but this is much easier said than done. The first gene therapy efforts focused on inherited disorders that researchers knew the most about, even though the conditions are very rare, because these would be the easiest to work with. Gene therapy efforts are now targeting more common illnesses, such as heart disease and cancers. **Tables 20.7** and **20.8** list some general requirements and concerns related to gene therapy.



Human gene  
cell culture



Enzyme  
replacement  
therapy



**Figure 20.2 Enzyme replacement therapy for Pompe disease has so far been very successful.** The human gene for acid alpha-glucosidase was attached to a casein (milk protein) promoter and produced in rabbit milk (in the Netherlands) and into Chinese hamster ovary cells (in the U.S.). Both approaches were tested on babies and led to improved symptoms, lowered muscle glycogen, improved muscle function, and hearts that returned to normal size. The drug, Myozyme, became available in 2006.

**Table 20.7**

### Gene Therapy Concerns

Scientific	Bioethical
<ol style="list-style-type: none"> <li>1. Which cells should be treated, and how?</li> <li>2. What proportion of the targeted cell population must be corrected to alleviate or halt progression of symptoms?</li> <li>3. Is overexpression of the therapeutic gene dangerous?</li> <li>4. Is it dangerous if the altered gene enters cells other than the intended ones?</li> <li>5. How long will the affected cells function?</li> <li>6. Will the immune system attack the introduced cells?</li> <li>7. Does the targeted DNA sequence occur in more than one gene?</li> </ol>	<ol style="list-style-type: none"> <li>1. Does the participant in a gene therapy trial truly understand the risks?</li> <li>2. If a gene therapy is effective, how will recipients be selected, assuming it is expensive at first?</li> <li>3. Should rare or more common disorders be the focus of gene therapy research and clinical trials?</li> <li>4. What effect should deaths among volunteers have on research efforts?</li> <li>5. Should clinical trials be halted if the delivered gene enters the germline?</li> </ol>

**Table 20.8**

### Requirements for Approval of Clinical Trials for Gene Therapy

1. Knowledge of defect and how it causes symptoms
2. An animal model
3. Success in human cells growing *in vitro*
4. No alternate therapies, or patients for whom existing therapies are not possible or have not worked
5. Safe experiments

## Variations on the Gene Therapy Theme

Gene therapy approaches vary in the way that healing genes are delivered and to which cells they are sent.

**Germline gene therapy** alters the DNA of a gamete or fertilized ovum. As a result, all cells of the individual have the change. Germline gene therapy is heritable—it passes to offspring. It is not being done in humans, although it creates the transgenic organisms discussed in chapter 19.

**Somatic gene therapy** corrects only the cells that an illness affects. It is nonheritable: A recipient does not pass the genetic correction to offspring. Clearing lungs congested from cystic fibrosis with a nasal spray containing functional CFTR genes is a type of somatic gene therapy.

Gene therapy approaches vary in invasiveness (**figure 20.3**). Cells can be altered outside the body and then infused, called

**ex vivo gene therapy**. In **in situ gene therapy**, the functional gene plus the DNA that delivers it (the vector) are injected into a very localized and accessible body part, such as a single melanoma skin cancer. In the most invasive approach, **in vivo** (“in the living body”) **gene therapy**, the vector is introduced directly into the body.

## Gene Delivery

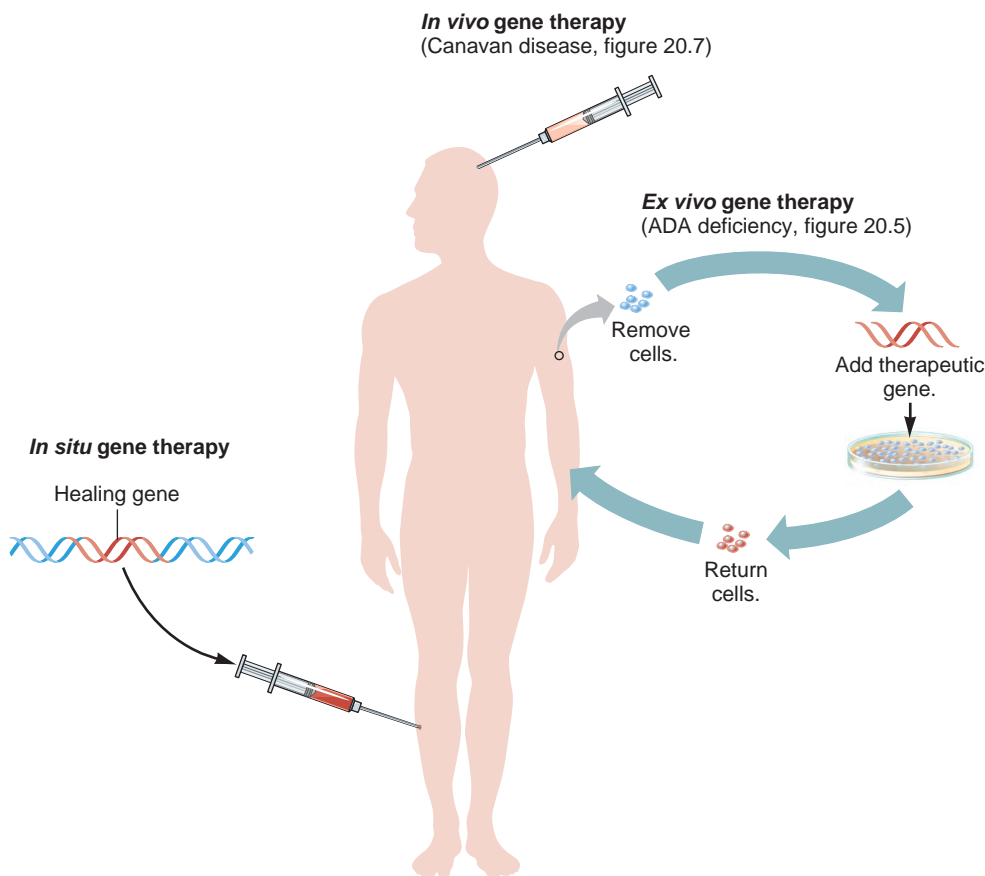
Researchers obtain therapeutic genes using the recombinant DNA and polymerase chain reaction technologies described in chapter 19. In the future, researchers and, someday, clinicians may deliver “artificial” genes synthesized on microchips.

Physical, chemical, and biological methods are used to send DNA into cells. Physical methods include electroporation, microinjection, and particle bombardment. Chemical methods include liposomes and

other types of lipids that carry DNA across the plasma membrane. The lipid carrier can penetrate the plasma membrane that DNA alone cannot cross, but it may not deliver a sufficient payload, and gene expression is only temporary.

Biological approaches to gene transfer use a vector, such as a viral genome. Researchers remove the viral genes that cause symptoms or alert the immune system and add the corrective gene. Different viral vectors are useful for different types of experiments. A certain virus may transfer its cargo with great efficiency but carry only a short DNA sequence. Another virus might carry a large piece of DNA but send it to many cell types, causing side effects. Or a virus may not infect enough cells to alleviate symptoms. Some retroviruses have limited use because they infect only dividing cells.

Some gene therapies can use viruses that normally infect the targeted cells. For example, adenoviruses that transport CFTR genes to the airway passages of people with cystic fibrosis normally infect lung tissue. In other cases, researchers can combine parts of viruses to target a certain cell type. Adeno-associated virus (AAV), for example, infects many cell types, but adding a promoter from a parvovirus gene restricts it to red blood cell progenitors in bone marrow. Add a human gene that encodes a protein normally found in red blood cells, and the entire vector can treat an inherited disorder of blood, such as sickle cell disease.



**Figure 20.3 Gene therapy invasiveness.** Therapeutic genes are delivered to cells removed from the body that are then returned (ex vivo gene therapy); delivered directly to an accessible body part such as skin (in situ gene therapy); or delivered directly to an interior body part, such as through the skull for Canavan disease or to an artery leading to the liver (in vivo gene therapy).

## Sites of Gene Therapy

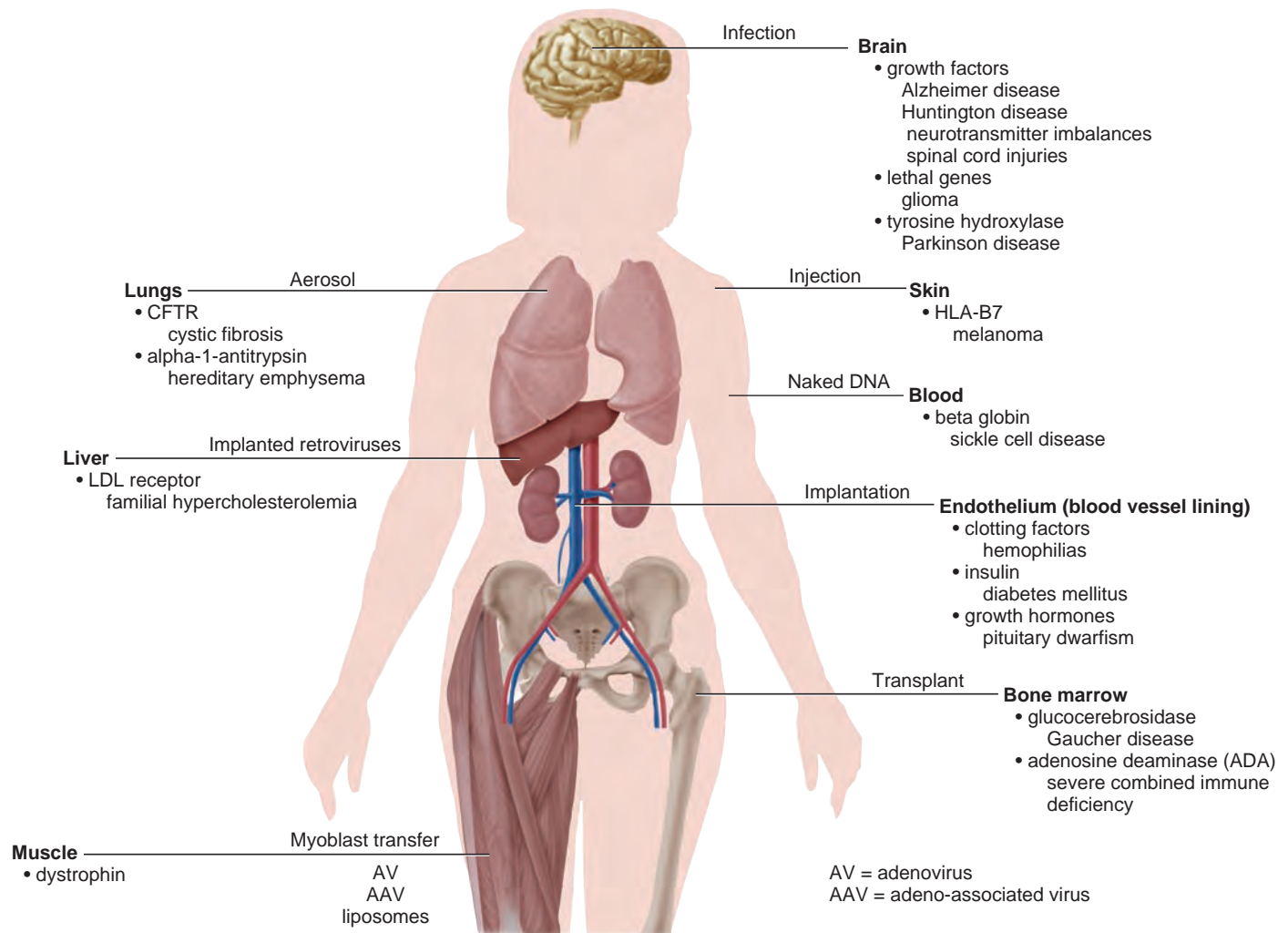
Several somatic gene therapies are in clinical trials, targeting several different tissues (**figure 20.4**). Gene delivery may be directly to the affected tissue, or into cells that can produce the needed protein and divide. Researchers are increasingly turning to stem and progenitor cells, because these cells can divide as well as travel.

Following are descriptions of some gene therapy targets under investigation.

**Endothelium** Endothelium forms capillaries. Genetically altered endothelium can secrete a needed protein directly into the bloodstream.

**Skin** Skin cells grow well. A person can donate a patch of skin the size of a letter on this page; after a genetic manipulation,





**Figure 20.4 Gene therapy sites.** Beneath the label for each site are listed the targeted protein (•) and then the disease.

the sample can grow to the size of a bath-mat within three weeks, and the skin can be grafted back onto the person. Skin grafts can be genetically modified to secrete therapeutic proteins.

**Muscle** Muscle tissue is a good target for gene therapy because it comprises about half of the body's mass, is easily accessible, and is near a blood supply. However, it is a challenge to correct enough muscle cells to alleviate symptoms.

**Liver** This largest organ is an important candidate for gene therapy because it has many functions and can regenerate. To treat some inborn errors, as little as 5 percent of the liver's 10 trillion cells would need to be corrected.

**Lungs** The respiratory tract is easily accessed with an aerosol spray, eliminating

the need to remove, treat, and reimplant cells. Several aerosols to treat cystic fibrosis replace the defective gene, but so far the correction is short-lived and localized.

**Nervous Tissue** Neurons are difficult targets because they do not divide. Gene therapy can alter other cell types, such as fibroblasts to secrete nerve growth factors or manufacture the enzymes necessary to produce certain neurotransmitters. Then the altered cells are implanted.

**Cancer** About half of current gene therapy trials target cancer. These approaches enable cancer cells, or their neighbors, to produce proteins that dampen oncogene expression, bolster tumor suppression, strengthen or redirect the immune response, or induce apoptosis.

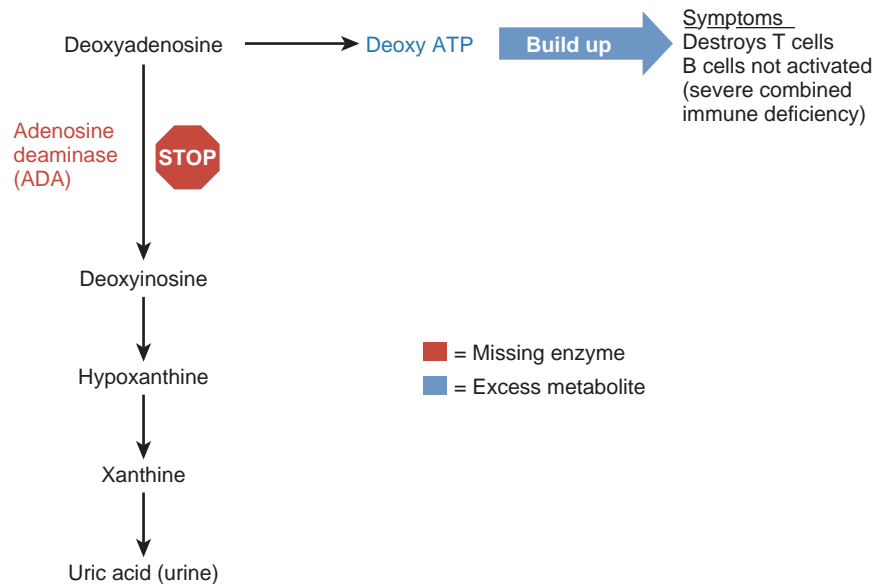
### Three Gene Therapies

Any new medical treatment begins with courageous volunteers who know that they may risk their health. Gene therapy, however, is unlike conventional drug therapy in that it attempts to alter an individual's genotype in a part of the body that has malfunctioned. Because the potentially therapeutic gene is usually delivered with other DNA, and it may be taken up by cell types other than those affected in the disease, reactions are unpredictable. Following is a look at some of the pioneers of gene therapy—the first patients.

**An Early Success** For the first few years of her life, Laura Cay Boren didn't know what it was like to feel well (**figure 20.5a**). From her birth in July 1982, she fought infection. Colds rapidly became pneumonia, and routine vaccines caused severe



a.



b.

**Figure 20.5 Correcting ADA deficiency.** (a) Laura Cay Boren spent much of her life in hospitals until she received the enzyme that her body lacks, adenosine deaminase (ADA). Here, she pretends to inject her doll as her mother looks on. Today, gene therapy is possible using cord blood stem cells. (b) ADA deficiency causes deoxy ATP to build up, destroying T cells, which therefore cannot stimulate B cells to secrete antibodies. The result is severe combined immune deficiency (SCID).

abscesses. In February 1983, doctors identified Laura's problem—severe combined immune deficiency (SCID) due to adenosine deaminase (ADA) deficiency.

Lack of ADA blocks a biochemical pathway that normally breaks down a metabolic toxin into uric acid, which is then excreted. The substance that ADA normally acts upon builds up and destroys T cells. Without helper T cells to stimulate B cells, no antibodies are made. The child becomes very prone to infections and cancer, and usually does not live beyond a year in the outside environment.

The Duke University Medical Center, where Laura celebrated her first and second birthdays, became her second home. In 1983 and 1984, she received bone marrow transplants from her father, which temporarily bolstered her immunity. Red blood cell transfusions also helped, but Laura was still spending more time in the hospital than out. By the end of 1985, she was gravely ill. She had to be fed through a tube, and repeated infection had severely damaged her lungs. Then Laura was chosen to participate in a trial for a new treatment, and in the spring of 1986, she received her first injection of PEG-ADA. This is the missing enzyme, ADA, from a cow and stabilized with polyethylene glycol (PEG) chains. (PEG is the major ingredient in antifreeze.)

Previous enzyme replacement without PEG didn't work, because what remained of the immune system destroyed the injected, unaltered enzyme. Patients needed frequent doses, which provoked the immune system further, causing severe allergic reactions. Laura's physicians hoped that adding PEG would keep ADA in her blood long enough to work.

Laura began responding to PEG-ADA almost immediately, and within hours, her enzyme level increased twentyfold. After three months, toxins no longer showed up in her blood, but her immunity was still suppressed. After six months, though, Laura's immune function neared normal for the first time ever—and stayed that way, with weekly doses of PEG-ADA. Her life changed dramatically as she ventured beyond the hospital's germ-free rooms. By summer 1988, she could finally play with other children without fear of infection. She began first grade in fall 1989, but had to repeat the year—she had spent her time socializing!

PEG-ADA revolutionized treatment of this form of SCID, but it replaced the protein, not the gene. The gene therapy approach began on September 14, 1990, at 12:52 P.M. Four-year-old Ashanthi DeSilva sat up in bed at the National Institute of Health in Bethesda, Maryland, and began receiving her own white blood cells intra-

venously. Earlier, doctors had removed the cells and inserted functioning ADA genes. The gene delivery worked, but did not alter enough cells to restore immunity. It had to be repeated, or PEG-ADA given at intervals. However, Ashanthi is now healthy, and she tells her story at scientific meetings (see *In Their Own Words* on page 405).

A longer-lasting treatment could result from altering progenitor T cells, which account for only one in several billion bone marrow cells. Umbilical cord blood was a more plentiful source. If fetuses who had inherited ADA deficiency could be identified, then stem cells could be extracted from their cord blood at birth, given ADA genes, and reinfused.

Crystal and Leonard Gobeia had already lost a five-month-old baby to ADA deficiency when amniocentesis revealed that their second fetus was affected. They and two other couples were asked to participate in an experiment. Andrew Gobeia and the other two babies received their own bolstered cord blood cells on the fourth day after birth, along with PEG-ADA to prevent symptoms in case the gene therapy did not work right away. T cells carrying normal ADA genes gradually appeared in their blood. By the summer of 1995, the three toddlers each had about 3 in 100 T cells carrying the ADA gene, and they continued to improve.



### The First Gene Therapy Patient

In the late 1980s, the DeSilva's did not think their little girl, Ashanthi ("Ashi"), would survive. She suffered near-continual coughs and colds, and was so fatigued that she could walk only a few steps before becoming winded, her father Raj recalls. "We took her to so many doctors that I stopped counting. One doctor after another would say it was asthma, an allergy, or bronchitis."

Raj's brother, an immunologist, suggested the blood tests that would eventually reveal Ashi's underlying problem—severe combined immune deficiency due to adenosine deaminase (ADA) deficiency. Although unlucky in inheriting a disease, Ashi was lucky in that it was a condition so well understood that it was first in line for gene therapy. Through a series of physician contacts, Ashi became the first recipient.

The medical team at the National Institute of Health—W. French Anderson, Kenneth Culver, and Michael Blaese—had



spent years planning the gene therapy, and were fairly certain that it would work.

Within weeks following the therapy, Ashi began to make her own, functional T cells. Although she required further treatments, today she is well and excited about her future, anticipating a career in the music industry after college.

Over the years, she has championed gene therapy at biomedical conferences. The photo shows her at a meeting when she was 17, where she introduced Dr. Blaese: "Our duty on Earth is to help others. I thank you from the bottom of my heart for all you have enabled me to do."

Gene therapy has hit snags in recent years, but overall has had an excellent track record. Says Dr. Blaese, "You have to consider the context. In the years since the first patient, there has been one death and two malignancies. Compare that to the first 100 heart transplants, where only one person lived more than a year. Gene therapy has had a remarkable safety record, yet there are still problems."

A few years after the three children with ADA deficiency were treated, another gene therapy trial for SCID began in France. Nine baby boys with a type of X-linked SCID had T cell progenitors removed and given the gene they were missing, which encodes part of a cytokine receptor. The therapy worked, but caused leukemia in three boys when the retrovirus that delivered the therapeutic gene inserted into a proto-oncogene. The boys were successfully treated for the leukemia, but this very unexpected side effect initially stalled many gene therapy trials. It was not the first time such an experiment had a tragic outcome. First came Jesse Gelsinger.

**A Major Setback** Eighteen-year-old Jesse Gelsinger died in September 1999, days after receiving gene therapy. An overwhelming immune response to the DNA used to introduce the therapeutic gene killed him.

Jesse had ornithine transcarbamylase deficiency (OTC) (OMIM 311250). In this X-linked recessive disorder, one of five enzymes required to break down amino

acids liberated from dietary proteins is absent (**figure 20.6**). The nitrogen released from the amino acids combines with hydrogens to form ammonia ( $\text{NH}_3$ ), which rapidly accumulates in the bloodstream and travels to the brain, with devastating effects. The condition usually causes irreversible coma within 72 hours of birth. Half of affected babies die within a month, and another quarter by age five. The survivors can control their symptoms by following a special low-protein diet and taking drugs that bind ammonia.

Jesse wasn't diagnosed until he was two, because he was a mosaic—some of his cells could produce the enzyme, so his symptoms were milder. When he went into a coma in December 1998 after missing a few days of his medications, he and his father considered volunteering for a gene therapy trial they had read about. When he turned 18, Jesse was tested at the University of Pennsylvania, and admitted to the trial. He was jubilant. He knew he might not directly benefit, but he had wanted to try to help babies who die

of the condition. A bioethics committee had advised that the experimental treatment not be tried on newborns because the parents would be too distraught to give informed consent. Instead, volunteers were older affected males and carrier females. Said Jesse at the time, "What's the worst that can happen to me? I die, and it's for the babies."

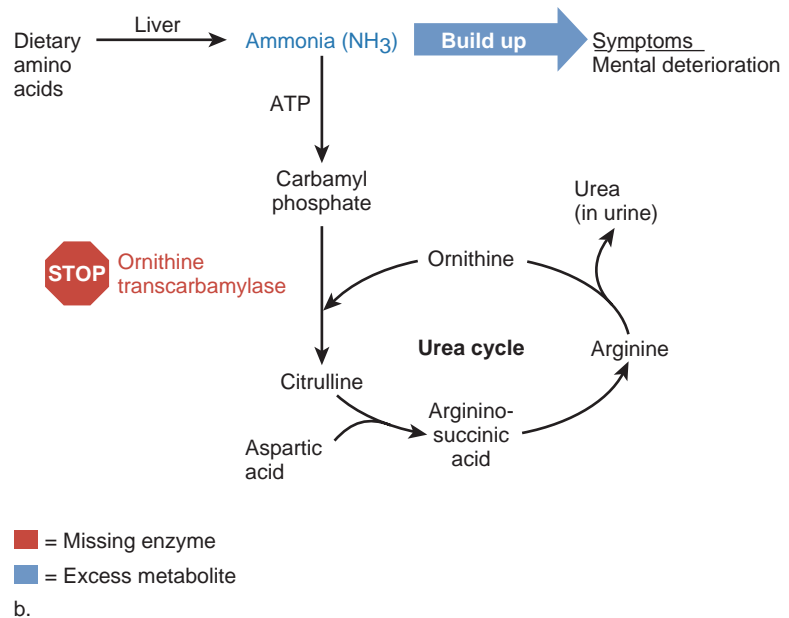
The gene therapy was an adenovirus with a functional human *OTC* gene inserted. This virus had already been used safely in about a quarter of the gene therapy experiments done since 1990. It is a disabled virus, with the genes that enable it to replicate and cause respiratory symptoms removed. Three groups of six patients each were to receive three different doses, to identify the lowest dose that would fight the OTC deficiency without side effects.

Jesse entered the hospital on Monday, September 13, after the 17 others in the trial had been treated and suffered nothing worse than fever and minor aches. Several billion altered viruses were placed in an artery leading into his liver. That night, Jesse





a.



b.

**Figure 20.6 A brave example.** (a) Jesse Gelsinger received gene therapy for an inborn error of metabolism in September 1999. He died four days later from an overwhelming immune response. (b) Lack of ornithine transcarbamylase causes ammonia to accumulate, which is toxic to the brain.

developed a high fever—still not unusual. But by morning, the whites of his eyes were yellow, indicating that his liver was struggling to dismantle the hemoglobin released from burst red blood cells. A flood of hemoglobin meant a flood of protein, so the ammonia level in his liver soon skyrocketed, reaching 10 times normal levels by mid-afternoon. Jesse became disoriented, then comatose. By Wednesday, doctors had controlled the ammonia buildup, but his lungs began to fail, and Jesse was placed on a ventilator. Thursday, vital organs began to fail, and by Friday, he was brain dead. His dedicated and devastated medical team stood by as his father turned off life support, and Jesse died.

The autopsy showed that Jesse had had a parvovirus infection, which may have led his immune system to attack the adenovirus. In the liver, the adenovirus had targeted not the hepatocytes as expected, but macrophages that function as sentries for the immune system. In response, interleukins flooded his body, and inflammation raged. Although parents of children with OTC implored government officials to continue to fund the research, the death of Jesse Gelsinger led to suspension of several gene therapy trials. The death drew particular attention to safety because, unlike most other volunteers, Jesse had not been very ill.

**A Success in the Making** Efforts begun in 1995 to treat Canavan disease continued, despite Jesse Gelsinger's fate. Canavan disease is an ideal candidate for gene therapy for several reasons:

1. The gene and protein are well known.
2. There is a window of time when affected children are healthy enough to be treated.
3. Only the brain is affected.
4. Brain scans can monitor response to treatment.
5. No treatment exists.

Canavan disease disrupts the interaction between neurons and neighboring cells called oligodendrocytes, which produce the fatty myelin that coats neurons, enabling them to transmit impulses fast enough for the brain to function (**figure 20.7**). Specifically, the brain neurons normally release N-acetylaspartate (NAA), which is broken down into harmless compounds by an enzyme, aspartoacylase, that the oligodendrocytes produce. In Canavan disease, the enzyme is missing, and the resulting NAA buildup destroys the oligodendrocytes. Without sufficient myelin, neurons cease to function, and developmental delay occurs, as happened to Max Randell, described in

the chapter opening essay. Due to a powerful founder effect, Canavan disease is seen almost exclusively in the Ashkenazi Jewish population. Bioethics: Choices for the Future relates the bitter battle over access to genetic tests for Canavan disease.

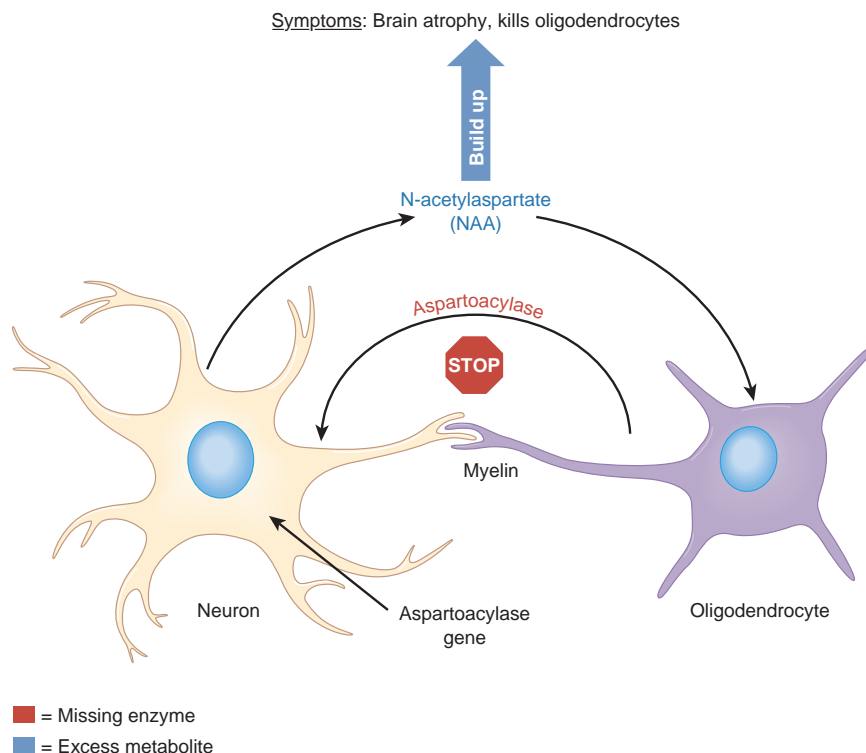
The first attempts at gene therapy for Canavan disease introduced the gene in a liposome, through holes bored into the skull. The first recipient, an 18-month-old, regained some skills for awhile. Previously, she could barely open her eyes and did not interact with anyone. But three months after the therapy, she looked around, moved, and vocalized. A brain scan showed neuron myelination in regions where it had vanished. She was not treated again until June 2001, when a viral vector replaced the liposomes. In the interim, while regulatory agencies argued about the safety of this therapy for a disease that had no other treatment, she lost some of the gains from the first round, such as being able to hold her head up. But the gene therapy does appear to be working in other children.

## Expectations and Limitations

When the age of gene therapy dawned in the 1990s, expectations were high—and for good reason. Work in the 1980s had clearly shown abundant, pure, human



a.



b.

**Figure 20.7 Canavan disease.** (a) Max Randell, shown here at two-and-a-half years old, in his “stander”, a device that keeps his body growing straight and strong. He underwent gene therapy that delivered viruses carrying a functional gene directly into his brain at six sites. Within ten days, he began to improve. (b) In Canavan disease, stripping of the lipid layer on brain neurons occurs because oligodendrocytes lack an enzyme that enables them to break down NAA which neurons produce. Buildup of NAA eventually destroys the oligodendrocytes, so that the neurons lack myelin. Gene therapy enables neurons to secrete the enzyme, restoring the fatty covering that makes nerve transmission possible in the brain. Other children have not done as well as Max.

biochemicals, useful as drugs, could come from genetically modified cells and transgenic organisms. It was a matter of time, many thought, before genetic altering of our own somatic tissue would treat a variety of ills.

In reality, gene therapy progress has been slow. Boys with Duchenne muscular dystrophy who receive immature muscle cells with healthy dystrophin genes do not walk again, although they might be able to wiggle a toe. People with cystic fibrosis who inhale viruses bearing the CFTR gene do not permanently breathe easier, but might feel relief for a few weeks. There have been other gene therapy deaths since Jesse Gelsinger.

The sequencing of the human genome did not provide a list of new gene defects to correct—many of the disease-causing genes were already known—but instead revealed a complexity to genome structure and function that will impact gene therapy. Consider the fact that the same exon sequence can be part of different genes. Targeting an exon because

it is part of one gene may affect others, healing one set of symptoms while causing others. As genome researchers continue to identify gene functions, this risk should lessen.

Discovery of RNA interference, discussed in chapter 11, may also complicate gene therapy. Correcting a genetic mistake in the nucleus may not counter a disease phenotype because of what may happen in the cytoplasm—the mRNA transcribed from the delivered gene may be silenced before the needed protein is even synthesized. Yet another area of uncertainty is the issue of somatic versus germline gene therapy. A corrected gene targeted to a particular tissue may find its way, in the circulation, to the reproductive tract, enter a gamete, and thereby affect the next generation.

Despite these drawbacks—real and theoretical—at a molecular and cellular level, gene therapy is working. The patients with muscular dystrophy, cystic fibrosis, and SCID have cells that have accepted

and expressed therapeutic genes. The challenge now is to find just the right vectors to deliver sustained, targeted, and safe genetic corrections.

## Key Concepts

1. Protein-based therapies replace gene products and treat the phenotype.
2. Gene therapies replace malfunctioning or absent genes.
3. Germline gene therapy targets gametes or fertilized ova and is heritable. Somatic gene therapy targets various types of somatic tissue as well as cancer cells and is not heritable.
4. Gene therapy may be *in situ*, *ex vivo*, or *in vivo*.
5. Vectors for delivering genes include liposomes and viruses.
6. Early gene therapies targeted ADA deficiency, OTC deficiency, and Canavan disease.



## Canavan Disease: Patients Versus Patents

When Debbie Greenberg gave birth to Jonathan in 1981, she and her husband Dan had no idea that they would one day lead the first effort to challenge how a researcher and a hospital patented a gene. Like Max Randell's parents, Debbie and Dan were each carriers of Canavan disease, and Jonathan was affected. Although Jonathan lived 11 years, his brain never developed past infancy. The couple had an affected daughter, Amy, a few years after Jonathan was born, and three healthy children.

Shortly after Jonathan's diagnosis, the Greenbergs started the Canavan Foundation, which established a tissue bank that stored blood, urine, and autopsy tissue from affected children. In 1987, the Greenbergs met Dr. Reuben Matalon at a Tay-Sachs disease screening event in Chicago, and convinced him to begin a search for the Canavan gene. The Greenbergs helped to collect tissue from families from all over the world, which was critical to Dr. Matalon's success in identifying

the gene and the causative mutation in 1993, when he was working at Miami Children's Hospital.

Finding the gene made it possible to detect the mutation. This could be used to confirm diagnoses, detect carriers, and test for the condition prenatally. By 1996, the Canavan Foundation was offering free testing. But unknown to the members of the organization who had donated their children's tissues for the gene search, Dr. Matalon and Miami Children's Hospital had filed for a patent on their discovery.

The U.S. Patent and Trademark office granted invention number 5,679,635—the Canavan gene—in 1997. A year later, the American College of Obstetricians and Gynecologists advised their physician members to offer carrier testing to Ashkenazi Jewish patients, because 1 in 40 such women is a carrier. Identifying couples in which both people are carriers would give them the option of avoiding giving

birth to affected children, a strategy that has reduced the number of children born with the similar Tay-Sachs disease to nearly zero. That same year, Miami Children's Hospital began to exercise its patent rights by requiring that doctors and diagnostic laboratories charge for a Canavan test. Suddenly, families whose donations—both monetary and biological—had made the discovery of the gene possible had to pay for carrier and prenatal tests. They were outraged.

On November 30, 2000, a group of parents and three nonprofit organizations filed suit in Chicago against Dr. Reuben Matalon and Miami Children's Hospital. The suit does not challenge the patent, but how it was obtained—in secret, they claim. They wish to recover earnings from the gene test to be turned over to the families who had to pay to offset licensing fees. In 2003, U.S. district judge Federico Morena upheld the rights of the parents to sue, calling the case “a tale of successful research collaboration gone sour.”

## Summary

### 20.1 Genetic Counseling

1. **Genetic counselors** provide information on inheritance patterns, disease risks and symptoms, and available tests and treatments.
2. Prenatal counseling and counseling a family coping with a particular disease pose different challenges.

### 20.2 Genetic Testing

3. Newborns are routinely screened for several inborn errors of metabolism, some of which are treatable.
4. Other genetic tests include prenatal diagnosis, cancer susceptibility tests, and predictive testing for genetic disease.

5. Direct-to-consumer genetic testing may provide incomplete information, or inappropriately extrapolate population data to individuals.
6. Genetic testing raises privacy issues when physicians must decide when it is appropriate to breach confidentiality about a test result.

### 20.3 Treating Genetic Disease

7. Enzyme replacement therapy uses recombinant DNA technology.
8. **Germline gene therapy** affects gametes or fertilized ova, affects all cells of an individual, and is transmitted to future generations. It is not performed in

humans. **Somatic gene therapy** affects somatic tissue and is not passed to offspring.

9. **Ex vivo gene therapy** is applied to cells outside the body that are then reimplanted or reinfused into the patient. **In situ gene therapy** occurs directly on accessible body parts. **In vivo gene therapy** is applied in the body.
10. Gene therapy delivers new genes and encourages production of a needed substance at appropriate times and in therapeutic (not toxic) amounts.
11. Several types of vectors are used to deliver therapeutic genes, including liposomes and viral genomes.



12. Some gene therapies target stem or progenitor cells, because they can divide and move.
13. There are many sites of somatic gene therapy, including cancers.

14. Development of gene therapy has been slower than anticipated because of the unexpected complexities of gene interactions and the challenge of

adequately targeting and sustaining therapeutic effects.

## Review Questions

1. Describe what a genetic counselor does.
2. What are the advantages and disadvantages of “virtual” genetic counseling (using an interactive computer program rather than a human)?
3. What factors do you think are important in deciding whether or not to provide populationwide newborn screening for a particular inherited disorder?
4. Why is newborn screening economically feasible?
5. Using information from this or other chapters, or the Internet, cite genetic tests given to a newborn, young adult, and middle-aged person (three different tests).
6. What are the three stages of the evolution of treatments for single-gene disorders?
7. Why is the removal of blood in people with hereditary hemochromatosis not gene therapy?
8. Explain the differences among *ex vivo*, *in situ*, and *in vivo* gene therapies. Give an example of each.
9. Would somatic gene therapy or germline gene therapy have the potential to affect evolution? Explain your answer.
10. What factors would a researcher consider in selecting a viral vector for gene therapy?
11. Why is it easier to “fix” a liver with gene therapy than to treat a muscle disease?
12. What are some of the complications that have slowed the development of gene therapy?
13. Compare the risks and potential benefits of gene therapy.

## Applied Questions

1. Choose one of the cases described in the chapter, and write out how you would counsel the family after the initial diagnosis.
2. Why would the American College of Medical Genetics ask that the government mandate testing for inborn errors of metabolism that do not have treatments?
3. What are the issues that a physician faces in deciding whether to violate confidentiality with a patient’s genetic test results?
4. A lentivirus is a rare type of retrovirus that can infect nondividing cells, therefore widening its applicability as a gene therapy vector. HIV is a lentivirus that is being evaluated in a disabled form as a vector for gene therapy. What would have to be done to it to make this feasible?
5. Parkinson disease is a movement disorder in which neurons in a part of the brain called the substantia nigra can no longer produce the neurotransmitter dopamine. This neurotransmitter is not a protein. What is a difficulty in developing gene therapy for Parkinson disease?
6. Create a gene therapy by combining items from the three lists below. Describe the condition to be treated, and how a gene therapy might correct the symptoms.

Cell Type	Vector	Disease Target
fibroblast	AV	Duchenne muscular dystrophy
skin cell	AAV	Alzheimer disease
neuroglial cell	retrovirus	sickle cell disease
red blood cell	liposome	cystic fibrosis
progenitor cell		
myoblast		

7. Genes can be transferred into the cells that form hair follicles. Would gene therapy to treat baldness most likely be *ex vivo*, *in situ*, or *in vivo*? Cite a reason for your answer.
8. Why might a gene therapy for Canavan disease be more likely to pass requirements of a bioethics review board than the trial that Jesse Gelsinger took part in?

### Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 20**, and **Web Activities** to find the website links needed to complete the following activities.

9. Use OMIM to identify a disease that might be treated with gene therapy, and describe how the therapy would work.
10. Consult a website dealing with newborn screening, and list three inherited conditions that can be detected as well as treated.

### Case Studies and Research Results

11. How would you, as a genetic counselor, handle the following situations (all real)? What would you tell the patients, and what tests would you suggest? (See other chapters for specific information.)
  - a. A couple in their early forties is expecting their first child. Amniocentesis indicates that the fetus is XXX, which might never have been noticed without the test. When they learn of the abnormality, the couple asks to terminate the pregnancy.
  - b. A 25-year-old woman gives birth to a baby with trisomy 21 Down syndrome. She and her husband are shocked—they thought that this could only happen to a woman over the age of 35.

- c. Two people of normal height have a child with achondroplastic dwarfism, an autosomal dominant trait. They are concerned that subsequent children will also have the condition.
- d. A newborn has a medical condition not associated with any known gene mutation or chromosomal aberration. The parents want to sue the genetics department of the medical center because the amniocentesis did not indicate a problem.
12. Two women are in the hospital suffering from emphysema. Linda, 20 years old, does not smoke. She has battled the condition all her life—she has an inherited form of emphysema called alpha-1-antitrypsin deficiency. She knows that she is unlikely to see her thirtieth birthday. Linda's roommate in the hospital, Bernice, is also struggling to breathe with emphysema. She is 58 years old and developed the condition from smoking since age 16. A pair of lungs becomes available for transplant, and they match the tissue types of both Linda and Bernice. If Linda has the transplant, the new lungs will eventually become diseased, because her underlying enzyme deficiency is still present. Still, she could gain a decade of life. If the lungs go to Bernice, they would likely stay healthy, as long as she does not smoke—which she is not certain she can do. What criteria should the transplant and bioethics teams consider to decide who receives the lungs?
13. Three-year-old Tawny Fitzgerald has been to the emergency department repeatedly for broken bones. At the last visit, a nurse questioned Tawny's parents, Donald and Rebecca, about possible child abuse. No charges were filed—the child just appeared to be clumsy. Then Tawny's brother Winston was born. When he was six months old, Donald found him screaming in pain one morning. A trip to the hospital revealed a broken arm. This time, a social worker was sent to the Fitzgerald home. Donald and Rebecca were interviewed in great depth and advised to find a lawyer. A relative in medical school suggested that they have the children examined for osteogenesis imperfecta, also known as “brittle bone disease.”
- Consult OMIM and list the facts about a form of this condition that could affect both sexes, with carrier parents. If you were the genetic counselor hired to help this couple, what would you ask them, and tell them, to help them deal with the legal and social services authorities who might need a biology lesson?
14. Jill and Scott S. had thought six-month-old Hannah was developing just fine until Scott's sister, a pediatrician, noticed that the baby's abdomen was swollen and hard. Knowing that the underlying enlarged liver and spleen could indicate an inborn error of metabolism, Scott's sister suggested the child undergo several tests. She had inherited sphingomyelin lipidosis, also known as Niemann-Pick disease type A (OMIM 257200). Both parents were carriers, but Jill had tested negative when she took a Jewish genetic disease panel during her pregnancy because her particular mutation was very rare and not included in the test panel. Hannah became the first child with Niemann-Pick disease to be successfully treated with a transplant of umbilical cord blood cells from a donor. As of her first birthday, she was catching up developmentally and was more alert than she would have been without the treatment. Monocytes, a type of white blood cell, from the cord blood traveled to her brain and manufactured the deficient enzyme. Dietary therapy does not work for this condition because the enzyme cannot cross from the blood to the brain. Monocytes, however, can enter the brain.
- Did Hannah's treatment alter her phenotype, genotype, or both?
  - Why did the transplant have to come from donated cord blood, and not from Hannah's own, which had been stored?
  - If you were the genetic counselor, what advice would you give this couple if they conceive again?
15. A survey conducted at Harvard Medical School of 1,250 mothers of children with Down syndrome found several instances when physicians delivered the diagnosis in extremely negative and upsetting language. The researcher offers suggestions on how doctors can be more sensitive in this situation, but concludes that only a physician should deliver such news. Suggest an alternative.
16. Lola sends \$300 to a genetic testing company along with a sample of her DNA to test for the MTHFR gene. She has a family history of heart disease, is overweight, and reads on the company website that elevated homocysteine in the blood has been associated with heart disease. MTHFR is an enzyme that keeps homocysteine from building up, which some gene variants do better than others. The most common mutant allele is called *C677T*. Individuals who have two copies of this allele are at elevated risk of cardiovascular disease. The website offers the following statistics:
- 5 to 10 percent of the general white population is homozygous recessive (has two copies of) the *C677T* variant.
  - 11 percent of white people who have venous thrombosis (blood clots in the veins) have the variant.
  - 17 percent of whites with coronary artery disease have the variant.
  - 19 percent of whites with arterial disease (not confined to the coronary arteries) have the variant.
- What additional information should Lola have to decide how to interpret her test results, which indicate that she is homozygous recessive for this mutation?
17. The Government Accounting Office's report on nutrigenetics testing can be found at [www.gao.gov/cgi-bin/getrpt?GAO-06-977T](http://www.gao.gov/cgi-bin/getrpt?GAO-06-977T). Read how the investigation was conducted.
- Do you think that the investigation was ethical?
  - Do you think that what the profiled companies offer is ethical?
  - Visit some of the nutrigenetics company websites, and write a short disclaimer that you would include to properly alert consumers to what the offered tests can and cannot provide.
18. Ashley X is a young girl who has static encephalopathy. She is bedridden, must be tube fed, and her parents cannot tell if she recognizes them. She is severely disabled. It isn't known whether the condition is inherited or not. Her parents have had her undergo several medical procedures and treatments to keep her small and childlike, because this will enable Ashley to remain at home as she ages. The media covered the case extensively, but it is helpful to read the primary sources:
- Ashley's parents account at <http://ashleytreatment.spaces.live.com/blog/>
  - “Attenuating Growth in Children with Profound Developmental Disability,” Daniel F. Gunther and Douglas S. Diekema, *Archives of Pediatrics & Adolescent Medicine*, vol. 160, no. 10, October 2006, pp 1013–1017.
- What is your opinion of what some bioethicists have termed “Peter Pan treatment”—trying to keep Ashley childlike?

# A Second Look

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1. Max Randell has Canavan disease and his brother Alex is a carrier. If the parents have another child, what is the chance that he or she will be free of the disease-causing allele? Canavan disease is autosomal recessive.
2. Does Max Randell's gene therapy alter his phenotype, genotype, or both?

3. Is his gene therapy germline or somatic?

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

- Gene doping
- Hemophilia B
- MCAD deficiency
- Rheumatoid arthritis gene therapy



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.





# Reproductive Technologies

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Intrafallopian Transfer  
Oocyte Banking and  
Donation  
Preimplantation Genetic  
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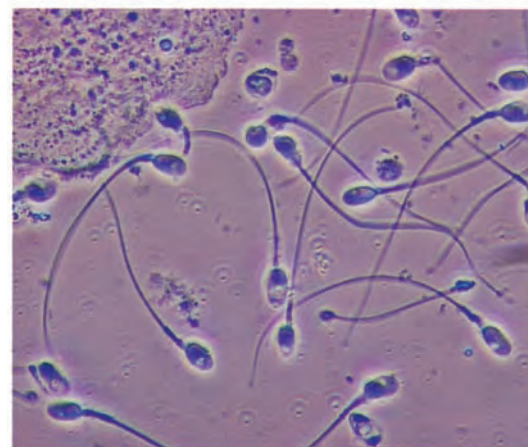
### 21.3 Extra Embryos

## POSTMORTEM SPERM RETRIEVAL

Bruce and Gaby V., in their early thirties, had delayed becoming parents, confident that their good health would make pregnancy possible later. But then Bruce suddenly died of an allergic reaction to a medication. Because she knew how much he had wanted to be a father, Gaby requested that physicians take some of Bruce's sperm after his death. Thirty hours after Bruce died, the medical examiner collected a sperm sample and sent it to the California Cryobank (a sperm bank), where it lay deeply frozen for more than a year. In the summer of 1978, Cappy Rothman, medical director of the bank, used the defrosted sperm to fertilize one of Gaby's oocytes. On March 17, their daughter was born. It was the first case of postmortem sperm retrieval in which the father did not actively participate in the decision. In other cases, the man was dying from cancer and had time to state his wishes to be a father posthumously. More recently, servicemen in the Gulf War in 1990–91 and in Operation Iraqi Freedom in 2003–5, fearing infertility from exposure to chemical or biological weapons, took advantage when sperm banks offered discounted sperm preservation to the military.

Postmortem sperm retrieval raises legal and ethical issues. In another case, in 1995, a woman conceived twins with her husband's consent sixteen months after her husband had died of leukemia at age 30. But the Social Security Administration refused to provide survivor benefits to their daughters, claiming that the father was not a father, but a sperm donor. The Massachusetts Superior Court reversed this decision. Because postmortem sperm retrieval, like other assisted reproductive technologies, is not regulated at the federal level in the United States, bioethicists have identified situations to avoid:

- Someone other than a spouse wishing to use the sperm
- A too-hasty decision based on grief
- Use of the sperm for monetary gain



Under what circumstances should sperm from a deceased soldier be used to conceive a child?

A couple in search of an oocyte donor advertises in a college newspaper seeking an attractive young woman from an athletic family. A cancer patient stores her oocytes before undergoing treatment. Two years later, she has several of them fertilized in a laboratory dish with her partner's sperm, and has a cleavage embryo implanted in her uterus. She survives the cancer and becomes a mother. A man paralyzed from the waist down has sperm removed and injected into his partner's oocyte. He, too, becomes a parent when he thought he never would.

Lisa and Jack Nash sought to have a child for a different reason. Their daughter Molly, born on July 4, 1994, had Fanconi anemia (OMIM 227650). This autosomal recessive condition would destroy her bone marrow and her immunity. An umbilical cord stem cell transplant from a sibling could likely cure her, but Molly had no siblings. Nor did her parents wish to have another child with a 1 in 4 chance of inheriting the disorder, as Mendel's first law dictates. Technology offered another solution.

In late 1999, researchers at the Reproductive Genetics Institute at Illinois Medical Center mixed Jack's sperm with Lisa's oocytes in a laboratory dish. After allowing 15 of the fertilized ova to develop to the 8-cell stage, researchers separated and applied DNA probes to one cell from each embryo. A cell that had wild type Fanconi anemia alleles and that matched Molly's human leukocyte antigen (HLA) type was identified and its 7-celled remainder



**Figure 21.1 Special siblings.** Adam Nash was conceived and selected to save his sister Molly's life. He is also a much-loved sibling and son. Several other families have since conceived one child to help another.

implanted into Lisa's uterus. Adam was born in late summer. A month later, physicians infused his umbilical cord stem cells into Molly, saving her life (**figure 21.1**).

Increased knowledge of how the genomes of two individuals come together and interact has spawned several novel ways to have children. **Assisted reproductive technologies** (ARTs) replace the source of a male or female gamete, aid fertilization, or provide a uterus. These procedures were developed to treat infertility, but are increasingly encompassing genetic screening. In the United States the government does not regulate ARTs.

## 21.1 Infertility and Subfertility

**Infertility** is the inability to conceive a child after a year of frequent intercourse without the use of contraceptives. Some specialists use the term *subfertility* to distinguish those individuals and couples who can conceive unaided, but for whom this may take longer than usual. On a more personal level, infertility is a seemingly endless monthly cycle of raised hopes and crushing despair. In addition to declining fertility, as a woman ages, the incidence of pregnancy-related problems rises, including chromosomal anomalies, fetal deaths, premature births, and low-birthweight babies. For most conditions, the man's advanced age does not raise the risk of pregnancy complications, although sperm motility declines with age.

Physicians who specialize in infertility treatment can identify a physical cause in 90 percent of cases. Of these, 30 percent of the time the problem is primarily in the male, and 60 percent of the time it is primarily in the female. When a physical problem is not obvious, the cause is usually a mutation or chromosomal aberration that impairs fertility in the male. The statistics are somewhat unclear, because in 20 percent of the 90 percent, both partners have a medical condition that could contribute to infertility or subfertility. A common combination is a woman with an irregular menstrual cycle and a man with a low sperm count.

One in six couples has difficulty in conceiving or giving birth to children. **Table 21.1** summarizes causes of subfertility and infertility.

## Male Infertility

Infertility in the male is easier to detect but sometimes harder to treat than female infertility. One in 25 men is infertile. Some men have difficulty fathering a child because they produce fewer than the average 120 million sperm cells per milliliter of ejaculate, a condition called oligospermia. It has several causes. If a low sperm count is due to a hormonal imbalance, administering the appropriate hormones may boost sperm output. Sometimes a man's immune system produces IgA antibodies that cover the sperm and prevent them from binding to oocytes. Male infertility can also be due to a varicose vein in the scrotum. This enlarged vein produces too much heat near developing sperm, and they cannot mature. Surgery can remove a scrotal varicose vein.

Most cases of male infertility are genetic. About a third of infertile men have small deletions of the Y chromosome that remove the only copies of key genes whose products control spermatogenesis. Other genetic causes of male infertility include mutations in genes that encode androgen receptors or protein fertility hormones, or that regulate sperm development or motility.

Sperm with extra chromosomes are ten times more likely to occur in men who had vasectomies reversed. Exactly how this happens isn't known, but it may be related to blocking the male reproductive system to keep developing sperm out of semen. If sperm with an abnormal number of chromosomes fertilize oocytes, the imbalance may end development so early that repeated pregnancy losses appear to be infertility.

For many men with low sperm counts, fatherhood is just a matter of time: They are subfertile, not infertile. If an ejaculate contains at least 60 million sperm cells, fertilization is likely eventually. To speed conception, a man with a low sperm count can donate several semen samples over a period of weeks at a fertility clinic. The samples are kept in cold storage, then pooled. Some of the seminal fluid is withdrawn to leave a sperm cell concentrate, which is then placed in the woman's body. It isn't very romantic, but it is highly effective at achieving pregnancy.

Sperm quality is more important than quantity. Sperm cells that are unable to move—a common problem—or are shaped abnormally, cannot reach an oocyte



Table 21.1

## Causes of Subfertility and Infertility

Men		
Problem	Possible Causes	Treatments
Low sperm count	Hormone imbalance, varicose vein in scrotum, possibly environmental pollutants Drugs (cocaine, marijuana, lead, arsenic, some steroids and antibiotics, chemotherapy) Oxidative damage Y chromosome gene deletions	Hormone therapy, surgery, avoiding excessive heat
Immobile sperm	Abnormal sperm shape  Infection Malfunctioning prostate Deficient apoptosis	Intracytoplasmic sperm injection Antibiotics Hormones
Antibodies against sperm	Problem in immune system	
Women		
Problem	Possible Causes	Treatment
Erratic ovulation	Pituitary or ovarian tumor Underactive thyroid Polycystic ovary syndrome	Surgery Hormone therapy Oral contraceptives
Antisperm secretions	Unknown	Acid or alkaline douche, estrogen therapy
Blocked uterine tubes	Infection caused by IUD, abortion, or by sexually transmitted disease	Laparotomy, oocyte removed from ovary and placed in uterus
Endometriosis	Unknown	Hormones, laparotomy, drugs

(figure 21.2). However, the genetic package of an immobile or abnormally shaped sperm cell can be injected into an oocyte. If the cause of male infertility is hormonal, however, replacing the absent hormones can sometimes make sperm move.

Hampered sperm motility is also associated with white blood cells in semen. The blood cells produce chemicals called reactive oxygen species, which bind sperm cell plasma membranes and destroy enzymes essential for the sperm cells to generate ATP. With too little ATP to supply energy, sperm cannot swim and fertility declines. Clinical trials are underway to test antioxidants to treat this form of male infertility.

Faulty apoptosis (programmed cell death) can also cause male infertility. Apoptosis normally kills abnormally shaped sperm. Men with high percentages of abnormally shaped sperm often have cell surface molecules that indicate impaired apoptosis.

## Female Infertility

Female infertility can be caused by abnormalities in any part of the reproductive system (figure 21.3). Many women with subfertility or infertility have irregular menstrual cycles, making it difficult to pinpoint when conception is most likely. In an average menstrual cycle of 28 days, ovulation usually occurs around the 14th day after menstruation begins, and this is when a woman is most likely to conceive.

For a woman with regular menstrual cycles who is under 30 years old and not using birth control, pregnancy typically happens within three or four months. A woman with irregular menstrual periods can use an ovulation predictor test, which detects a peak in the level of luteinizing hormone that precedes ovulation by a few hours. Another way to detect the onset of ovulation is to record body temperature



a.

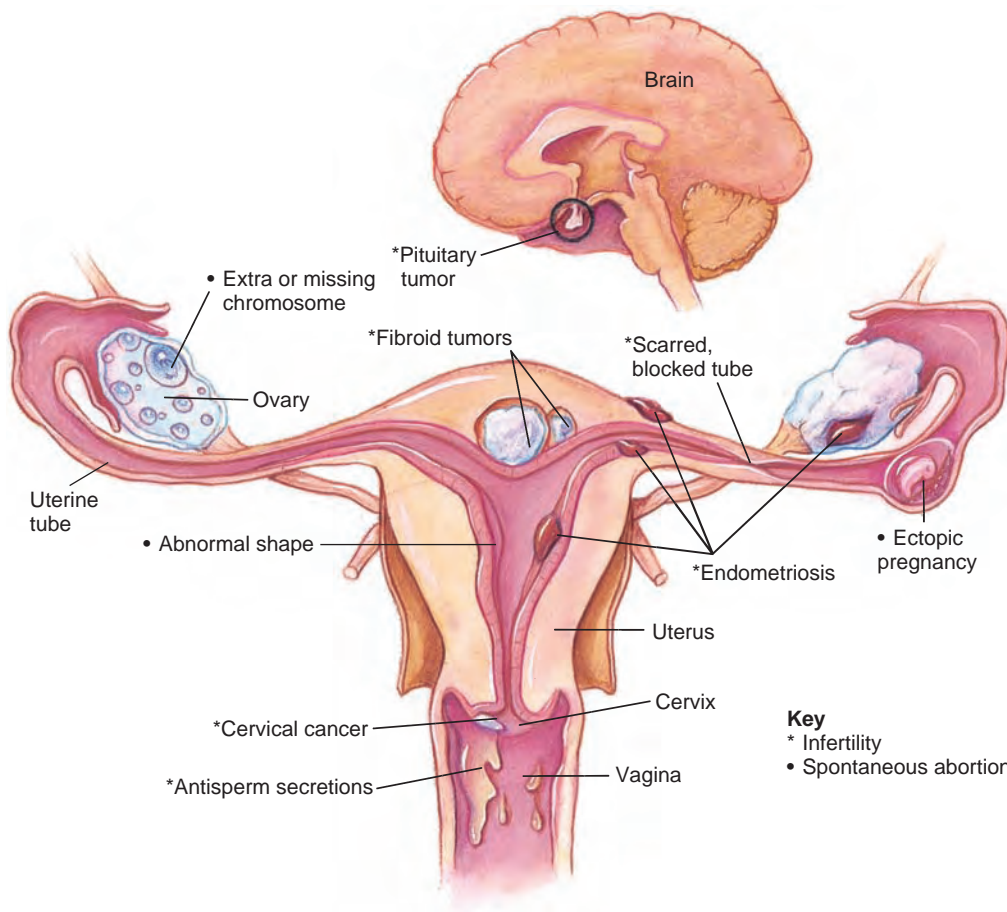


b.

**Figure 21.2 Sperm shape and motility are important.** (a) Healthy sperm in action. (b) A misshapen sperm cannot fertilize an oocyte.

each morning using a digital thermometer with subdivisions of hundredths of a degree Fahrenheit, which can indicate the 0.4 to 0.6 rise in temperature that occurs when ovulation starts. This is when a woman is at her most fertile. She can then time intercourse for when she is most likely to conceive. Sperm can survive in a woman's body for up to five days, but the oocyte is only viable for 24 to 48 hours after ovulation.

The hormonal imbalance that usually underlies irregular ovulation has various causes. These include a tumor in the ovary or in the pituitary gland in the brain that controls the reproductive system, an underactive thyroid gland, or use of steroid-based drugs such as cortisone. Sometimes a woman produces too much prolactin, the hormone that promotes milk production



**Figure 21.3** Sites of reproductive problems in the female.

and suppresses ovulation in new mothers. If prolactin is abundant in a nonpregnant woman, she will not ovulate.

Fertility drugs can stimulate ovulation, but they can also cause women to “super-ovulate,” producing more than one oocyte each month. A commonly used drug, clomiphene, raises the chance of having twins from 1 to 2 percent to 4 to 6 percent. If a woman’s ovaries are completely inactive or absent (due to a birth defect or surgery), she can become pregnant only if she uses a donor oocyte.

A common cause of female infertility is blocked uterine tubes. Fertilization usually occurs in open tubes. Blockage can prevent sperm from reaching the oocyte, or entrap a fertilized ovum, keeping it from descending into the uterus. If an embryo begins developing in a blocked tube and is not removed and continues to enlarge, the tube can burst and the woman can die. Such a “tubal pregnancy” is called an ectopic pregnancy.

Uterine tubes can also be blocked due to a birth defect or, more likely, from an infection such as pelvic inflammatory disease. A woman may not know she has blocked uterine tubes until she has difficulty conceiving and medical tests uncover the problem. Surgery can sometimes open blocked uterine tubes.

Excess tissue growing in the uterine lining may make it inhospitable to an embryo. This tissue can include benign tumors called fibroids or areas of thickened lining from a condition called endometriosis. In response to the hormonal cues to menstruate, the lining bleeds, causing cramps. Endometriosis can hamper conception, but curiously, if a woman with endometriosis conceives, the cramps and bleeding usually disappear after the birth.

Sometimes secretions in the vagina and cervix are hostile to sperm. If cervical mucus is unusually thick or sticky, as can happen during infection, sperm become entrapped

and cannot move far enough to encounter an oocyte. Vaginal secretions may be so acidic or alkaline that they weaken or kill sperm. For example, some women with cystic fibrosis are unable to secrete bicarbonate from the cells lining their reproductive tracts, which is normally required to activate sperm. Douching daily with an acidic solution such as acetic acid (vinegar) or an alkaline solution, such as bicarbonate, can alter the pH of the vagina so that in some cases it is more receptive to sperm cells. Too little mucus is treated with low daily doses of oral estrogen. Sometimes mucus in a woman’s body harbors antibodies that attack sperm. Infertility may also result if the oocyte fails to release sperm-attracting biochemicals.

One reason female infertility increases with age is that older women are more likely to produce oocytes with an abnormal chromosome number, which often causes spontaneous abortion because defects are too severe for development to proceed for long. Losing very early embryos may appear to be infertility because the bleeding accompanying the aborted embryo resembles a heavy menstrual flow. The higher incidence of meiotic errors in older women may occur because their oocytes have been exposed longer to harmful chemicals, viruses, and radiation.

## Infertility Tests

A number of medical tests can identify causes of infertility. The man is checked first, because it is easier, less costly, and less painful to obtain sperm than oocytes.

Sperm are checked for number (sperm count), motility, and morphology (shape). An ejaculate containing up to 40 percent unusual forms is still considered normal, but many more than this can impair fertility. A urologist performs sperm tests. A genetic counselor may also be of help in identifying the cause of male infertility by interpreting results of a PCR analysis of the Y chromosome to detect deletions associated with lack of sperm. If a male cause of infertility is not apparent, the next step is for the woman to consult a gynecologist, who checks to see that the structures of the reproductive system are present and functioning.

Some cases of subfertility or infertility have no clear explanation. Psychological factors may be at play, or it may be that inability to conceive results from

consistently poor timing. Sometimes a sub-fertile couple adopts a child, only to conceive one of their own shortly thereafter; many times, infertility remains a lifelong mystery.

### Key Concepts

- 1. Male infertility is due to a low sperm count or sperm that cannot swim or are abnormal in structure.
- 2. Female infertility can be due to an irregular menstrual cycle or blocked uterine tubes. Fibroid tumors, endometriosis, or a misshapen uterus may prevent implantation of a fertilized ovum, and secretions in the vagina and cervix may inactivate or immobilize sperm. Oocytes may fail to release a sperm-attracting biochemical.
- 3. Early pregnancy loss due to abnormal chromosome number may be mistaken for infertility; this is more common among older women.
- 4. A variety of medical tests can pinpoint some causes of infertility.

## 21.2 Assisted Reproductive Technologies

Many people with fertility problems use alternative ways to conceive. Several of the ARTs were developed in nonhuman animals

(see the Technology Timeline on page 418). In the United States, about 1 percent of the approximately 4 million births a year are from ARTs. The ART births account for 0.4 percent of single births and 16 percent of multiples, reflecting the fact that usually more than one fertilized ovum is implanted.

This section describes types of ARTs. The different procedures can be performed on material from the parents-to-be (“non-donor”) or from donors, and may be “fresh” (collected just prior to the procedure) or “frozen” (preserved in liquid nitrogen). **Table 21.2** compares the success rates of the different ARTs for several hundred fertility clinics in the United States.

### Donated Sperm—Intrauterine Insemination

The oldest assisted reproductive technology is **intrauterine insemination (IUI)**, in which a doctor places donated sperm into a woman’s cervix or uterus. (It used to be called artificial insemination.) The sperm are first washed free of seminal fluid, which can inflame female tissues. Her partner may be infertile or carry a gene for an inherited illness that the couple wishes to avoid passing to their child, or a woman may undergo IUI if she desires to be a single parent without having sex.

The first documented IUI in humans was done in 1790. For many years, physicians

donated sperm, and this became a way for male medical students to earn a few extra dollars. By 1953, sperm could be frozen and stored and IUI became much more commonplace. Today, donated sperm are frozen and stored in sperm banks, which provide the cells to obstetricians who perform the procedure. IUI costs about \$125. However, if ovulation is induced to increase the chances of success, additional costs may exceed \$3,000.

A couple who chooses IUI can select sperm from a catalog that lists the personal characteristics of donors, such as blood type, hair and eye color, skin color, build, and even educational level and interests. One donor profile listed that the man enjoyed spear-fishing and wrestling, listens to singer Tori Amos, and loves the film *The Princess Bride*—as if these are inherited traits. Many women selected him because he was a handsome doctor! If a couple desires a child of one sex—such as a daughter to avoid passing on an X-linked disorder—sperm can be separated into fractions enriched for X-bearing or Y-bearing sperm.

Problems can arise in IUI if a donor learns that he has an inherited disease. For example, a man who donated sperm years ago developed cerebellar ataxia (OMIM 608029), a movement disorder. Eighteen children conceived using his sperm face a 1 in 2 risk of having inherited the mutant gene. In 1983, the Sperm Bank of California became the first to ask donors if they wished

**Table 21.2**  
Comparison of Assisted Reproductive Technologies

Number of:	Technologies						
	Embryo transfer to host (surrogate)	IVF (fresh, nondonor)	IVF (frozen, nondonor)	IVF (fresh, donor)	IVF (frozen, donor)	GIFT	ZIFT
Treatments	1,210	73,406	13,083	7,581	2,721	549	763
Retrievals	1,114	62,881	NA	6,929	NA	489	683
Transfers	1,066	59,004	11,394	6,684	2,395	477	604
Pregnancies	459	22,567	2,906	3,413	704	162	242
Deliveries	382	18,793	2,324	2,920	563	121	204
Success rate	~32%	~26%	~18%	~39%	~21%	~22%	~22%

Retrieval = removing oocyte or fertilized ovum from woman

NA = not applicable (frozen embryos are not retrieved)

(Data from a large sample of fertility clinics)

IVF = *in vitro* fertilization

GIFT = gamete intrafallopian transfer

ZIFT = zygote intrafallopian transfer



# Technology Timeline

## Landmarks in Reproductive Technology

### In Nonhuman Animals

### In Humans

1782	Intrauterine insemination in dogs	
1790		Pregnancy reported from intrauterine insemination
1890s	Birth from embryo transplantation in rabbits	Intrauterine insemination by donor
1949	Cryoprotectant successfully freezes animal sperm	
1951	First calf born after embryo transplantation	
1952	Live calf born after insemination with frozen sperm	
1953		First reported pregnancy after insemination with frozen sperm
1959	Live rabbit offspring produced from <i>in vitro</i> (“test tube”) fertilization (IVF)	
1972	Live offspring from frozen mouse embryos	
1976		First reported commercial surrogate motherhood arrangement in the United States
1978	Transplantation of ovaries from one cow to another	Baby born after IVF in United Kingdom
1980		Baby born after IVF in Australia
1981	Calf born after IVF	Baby born after IVF in United States
1982	Sexing of embryos in rabbits	
	Cattle embryos split to produce genetically identical twins	
1983		Embryo transfer after uterine lavage
1984		Baby born in Australia from frozen and thawed embryo
1985		Baby born after gamete intrafallopian transfer (GIFT)
		First reported gestational surrogacy arrangement in the United States
1986		Baby born in the United States from frozen and thawed embryo
1989		First preimplantation genetic diagnosis (PGD)
1992		First pregnancies from sperm injected into oocytes
1994	Intracytoplasmic sperm injection (ICSI) in mouse and rabbit	62-year-old woman gives birth from donated oocyte
1995	Sheep cloned from embryo cell nuclei	Babies born following ICSI
1996	Sheep cloned from adult cell nucleus	
1998	Mice cloned from adult cell nuclei	
1999	Cattle cloned from adult cell nuclei	Baby born 7 years after his twin
2000	Pigs cloned from adult cell nuclei	
2001		Sibling born following PGD to treat sister for genetic disease
		Human preimplantation embryo cloned, survives to 6 cells
2003		3000 <sup>+</sup> preimplantation genetic diagnoses performed to date
2004	Woman pays \$50,000 to have her cat cloned	First birth from a woman who had ovarian tissue preserved and implanted on an ovary after cancer treatment.
2005	Dog cloned	

to be contacted by their children years later. In 2002, the first such meeting occurred, evidently quite successfully. Today, a website (<http://www.donorsiblingregistry.com>) enables half-siblings who share sperm donor fathers to meet. Thousands have already done so. Each year about 30,000 newborns trace their beginnings to intra-uterine insemination.

A male's role in reproductive technologies is simpler than a woman's. A man can be a genetic parent, contributing half of his genetic self in his sperm, but a woman can be both a genetic parent (donating an oocyte) and a gestational parent (donating the uterus). Problems can arise when a second female assists in conception and/or gestation.

## A Donated Uterus—Surrogate Motherhood

If a man produces healthy sperm but his partner's uterus cannot maintain a pregnancy, a surrogate mother may help by being inseminated with the man's sperm. When the child is born, the surrogate mother gives the baby to the couple. In this variation of the technology, the surrogate is both the genetic and the gestational mother. Attorneys usually arrange surrogate relationships. The surrogate mother signs a statement signifying her intent to give up the baby, and she is paid for her nine-month job.

The problem with surrogate motherhood is that a woman may not be able to predict her responses to pregnancy and childbirth in the cold setting of a lawyer's office months earlier. When a surrogate mother changes her mind about giving up the baby, the results are wrenching for all. A prominent early case involved Mary Beth Whitehead, who carried the child of a married man for a fee and then changed her mind about relinquishing the baby. Whitehead's ties to "Baby M" were perhaps stronger because she was both the genetic and the gestational mother.

Another type of surrogate mother lends only her uterus, receiving a fertilized ovum conceived from a man and a woman who has healthy ovaries but lacks a functional uterus. This variation is an "embryo transfer to a host uterus." The gestational-only surrogate mother turns the child over to the biological parents.

## In Vitro Fertilization

In *in vitro* fertilization (IVF), which means "fertilization in glass," sperm and oocyte join in a laboratory dish. Soon after the embryo that forms is placed in the oocyte donor's uterus (or another woman's uterus). If all goes well, it implants into the uterine lining.

Louise Joy Brown, the first "test-tube baby," was born in 1978. Initial media attention was great, with cartoons depicting a newborn with the word "Pyrex," a test-tube and glassware manufacturer, branded on her thigh. A bioethicist said that IVF challenged "the idea of humanness and of our human life and the meaning of our embodiment and our relation to ancestors and descendants." Yet Louise is, despite her unusual beginnings, an ordinary young woman. IVF has since led to the births of more than a million children.

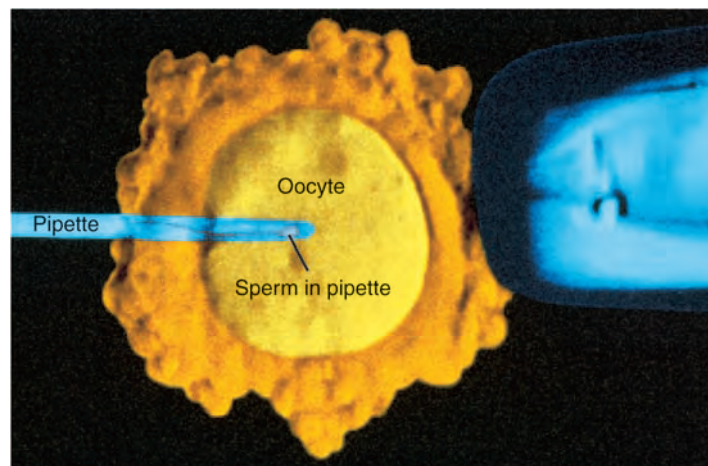
A woman might undergo IVF if her ovaries and uterus work but her uterine tubes are blocked. Using a laparoscope, which is a lit surgical instrument inserted into the body through a small incision, a physician removes several of the largest oocytes from an ovary and transfers them to a culture dish. If left in the body, only one oocyte would exit the ovary, but in culture, many can mature sufficiently to be fertilized *in vitro*. Sperm and chemicals similar to those in the female reproductive tract are added to the culture. An acidic solution

may be applied to the zona pellucida, the layer around the egg, to thin it to "assist hatching."

If the sperm cannot readily penetrate the oocyte, they may be sucked up into a tiny syringe and microinjected into the female cell. Called **intracytoplasmic sperm injection** (ICSI), this technique is more effective than IVF alone (**figure 21.4**). ICSI is very helpful for men who have low sperm counts or many abnormal sperm. The procedure even works with immature sperm. With ICSI, fatherhood is possible for men who cannot ejaculate, such as those who have suffered spinal cord injuries. ICSI has been very successful, performed on thousands of men with about a 30 percent success rate. The Bioethics: Choices for the Future on page 420 considers a problem with ICSI—transmitting infertility.

A day or so after sperm wash over the oocytes in the dish, or are injected into them, one or two of the embryos—balls of 8 or 16 cells—are transferred to the woman's uterus. If the hormone human chorionic gonadotropin appears in her blood a few days later, and its level rises, she is pregnant.

IVF costs from \$6,500 to \$15,000 per attempt. The success rate is lower than for embryos conceived through sexual intercourse because of the difficulty of the procedure and because couples who choose IVF are more likely to have subfertility or infertility than the general population. Children born following IVF have twice



**Figure 21.4 ICSI.** Intracytoplasmic sperm injection (ICSI) enables some infertile men, men with spinal cord injuries, or men with certain illnesses to become fathers. A single sperm cell is injected into the cytoplasm of an oocyte. This photo is falsely colored.



## Technology Too Soon? The Case of ICSI

Intracytoplasmic sperm injection (ICSI), available since 1995, has been extremely successful in enabling men with AIDS, paralysis, very low sperm counts, or abnormal sperm to become fathers. The birth defect rate is about the same as for non-ICSI IVF. But as more ICSI procedures are performed and tests on nonhuman animals continue, potential problems are emerging, based on the fact that ICSI bypasses what one researcher calls “natural sperm selection barriers.”

ICSI is now commonly used on men who have azoospermia—lack of sperm—or oligospermia—very few sperm. The rare sperm are sampled from an ejaculate or taken from the testes with a needle, then injected into an oocyte. Sometimes these men produce spermatids but not mature sperm, and spermatids that have already elongated can also successfully fertilize oocytes using ICSI. However, a complication has developed that involves not science, but logic. About 10 percent of infertile men have microdeletions in the Y chromosome. When their sperm cells are used in ICSI, they pass on the infertility to their sons. This is true for other causes of infertility and subfertility, too. For example, if a man’s above-average proportion of abnormally shaped sperm is due to abnormal apoptosis, he could pass a susceptibility to cancer to his offspring.

Bioethicists are debating whether it is right to intentionally conceive a male who

is genetically destined to be infertile. On the positive side is the opportunity ICSI is providing to study that infertility. It is possible that adolescents with Y chromosome microdeletions can produce viable sperm or spermatids, and if so, these cells can be sampled and stored for later use. In the past, these men would not have suspected that they had Y chromosome abnormalities until they had difficulty fathering children. Alternatives to transmitting deletions and other mutations include selecting and using only X-bearing sperm in ICSI, or selecting and implanting only female fertilized ova. Because of the transmission of Y-linked infertility with ICSI, men undergoing fertility testing and considering the procedure now have their Y chromosomes screened for deletions, and genetic counseling is provided.

Experiments on rhesus monkeys are pinpointing the sources of damage to ICSI embryos that cease developing:

- Injecting sperm at the site of the polar body on the oocyte can disrupt the meiotic spindle, leading to nondisjunction (an extra or missing chromosome).
- Injected sperm DNA does not always condense properly, also leading to nondisjunction.
- Spermatids that have not yet elongated are often unable to fertilize an oocyte. Culturing them in the laboratory

until they mature may help improve the odds of success.

- Spermatids may not be completely imprinted, leading to problems in gene expression.
- Mitotic cell cycle checkpoints are altered at the first division following ICSI.
- Injected sperm sometimes lack a protein that normally associates with the sex chromosomes. This may explain an elevation in sex chromosome anomalies among ICSI children.
- Injected sperm can include surface proteins normally left outside the oocyte, producing unanticipated effects. They may also include mitochondria from the male.

Despite these largely theoretical concerns, parents of children conceived with ICSI do not have any cause to worry, researchers insist. Tests on these children so far have not revealed any problems. Says one researcher, “In spite of its potential risks, ICSI still seems to be remarkably safe.” Still, it would be comforting to some to have more research to back up this new way to start development. Ongoing studies are following the children of ICSI for longer times, and investigating any correlations between health problems in offspring and the cause of subfertility or infertility in the fathers.

the rate of birth defects (about 9 percent) compared to children conceived naturally, which may also reflect the underlying medical problems of parents seeking the procedure.

In the past, several embryos were implanted to increase the success rate of IVF, but this led to many multiple births. In many cases, embryos had to be removed to make room for others to survive. To avoid the multiples problem, clinicians began

transferring only two embryos, and more recently, just one, after a study showed very similar birth rates for one or two.

Measures to improve the chance that IVF will culminate in a birth include:

1. Transferring embryos at the blastocyst stage.
2. Culturing fertilized ova and early embryos with other cells that normally surround the oocyte in the ovary.

These “helper” cells provide extra growth factors.

3. Screening early embryos for chromosome abnormalities, and implanting only those with normal karyotypes.

Embryos resulting from IVF that are not soon implanted in the woman are frozen in liquid nitrogen, with cryoprotectant chemicals added to prevent salts from building up or ice crystals from damaging delicate cell



parts. Freezing takes a few hours; thawing about a half hour. The longest an embryo has been frozen, stored, and then successfully revived is 13 years; the “oldest” pregnancy using a frozen embryo occurred 9 years after the freezing!

## Gamete and Zygote Intrafallopian Transfer

IVF may fail because of the artificial environment for fertilization. A procedure called GIFT, which stands for **gamete intrafallopian transfer**, improves the setting. (Uterine tubes are also called fallopian tubes). Fertilization is assisted in GIFT, but it occurs in the woman’s body rather than in glassware.

In GIFT, a woman has several of her largest oocytes removed. The man submits a sperm sample, and the most active cells are separated from it. The collected oocytes and sperm are deposited together in the woman’s uterine tube, at a site past any obstruction that might otherwise block fertilization. GIFT is about 22 percent successful, and usually costs less than IVF.

A variation of GIFT is ZIFT, which stands for **zygote intrafallopian transfer**. In this procedure, an IVF ovum is introduced into the woman’s uterine tube. Allowing the fertilized ovum to make its own way to the uterus increases the chance that it will implant. ZIFT is 22 percent successful.

GIFT and ZIFT are done less frequently than IVF. They often will not work for women who have scarred uterine tubes.

## Oocyte Banking and Donation

Oocytes can be stored, as sperm are, but the procedure may introduce problems. An oocyte contains a large volume of water. Freezing can cause ice crystals to form that can damage cell parts. Candidates for preserving oocytes for later use include women who wish to have children later in life and women exposed to toxins or teratogens in the workplace or in chemotherapy.

Oocytes are frozen in liquid nitrogen at  $-30$  to  $-40$  degrees Celsius, when they are at metaphase of the second meiotic division. At this time, the chromosomes are

aligned along the spindle, which is sensitive to temperature extremes. If the spindle comes apart as the cell freezes, the oocyte may lose a chromosome, which would devastate development. Another problem with freezing oocytes is retention of a polar body, leading to a diploid oocyte. Only 100 babies have been born using frozen oocytes despite two decades of attempts. The probability of pregnancy using a frozen oocyte with current technology is only about 3 percent.

To avoid the difficulty of freezing oocytes, strips of ovarian tissue can be frozen, stored, thawed, and reimplanted at various sites, such as under the skin of the forearm or abdomen or in the pelvic cavity near the ovaries. The first child resulting from fertilization of an oocyte from reimplanted ovarian tissue was born in 2004. The mother, age 25, had been diagnosed with advanced Hodgkin’s lymphoma in 1997. The harsh chemotherapy and radiation cured her cancer, but destroyed her ovaries. Five strips of tissue from her left ovary were frozen and in 2003 several pieces of ovarian tissue were thawed and implanted in a pocket that surgeons crafted on one of her shriveled ovaries, very near the entrance to a uterine tube. Menstrual cycles resumed, and shortly thereafter, the woman became pregnant with her daughter, who is healthy. Freezing ovarian tissue is likely to become routine for cancer patients of childbearing age.

Women can also obtain oocytes from donors, typically younger women. Often these women are undergoing IVF and have “extra” harvested oocytes (see the opening essay for chapter 3 on oocyte donation). The potential father’s sperm and donor’s oocytes are placed in the recipient’s uterus or uterine tube, or fertilization occurs in the laboratory, and an 8- or 16-celled embryo is transferred to the woman’s uterus.

The first baby to result from oocyte donation was born in 1984. The success rate ranges from 20 to 50 percent, and the procedure costs at least \$10,000. The technique is useful for the reasons cited for freezing oocytes, as well as to avoid transmitting a disease-causing gene.

Embryo adoption is a variation on oocyte donation. A woman with malfunctioning

ovaries but a healthy uterus carries an embryo that results when her partner’s sperm is used in intrauterine insemination of a woman who produces healthy oocytes. If the woman conceives, the embryo is gently flushed out of her uterus a week later and inserted through the cervix and into the uterus of the woman with malfunctioning ovaries. The child is genetically that of the man and the woman who carries it for the first week, but is born from the woman who cannot produce healthy oocytes. “Embryo adoption” is also the term used to describe use of IVF “leftovers.”

In another technology, cytoplasmic donation, older women have their oocytes injected with cytoplasm from the oocytes of younger women to “rejuvenate” the cells. Although resulting children conceived through IVF appear to be healthy, they are being monitored for a potential problem—heteroplasmy, or two sources of mitochondria in one cell. Researchers do not yet know the health consequences of having mitochondria from the donor cytoplasm plus mitochondria from the recipient’s oocyte. These conceptions also have an elevated incidence of XO syndrome, which often causes spontaneous abortion.

Because oocytes are harder to obtain than sperm, oocyte donation technology has lagged behind that of sperm banks, but is catching up. One IVF facility that has run a donor oocyte program since 1988 has a patient brochure that describes 120 oocyte donors of various ethnic backgrounds, like a catalog of sperm donors. The oocyte donors are young and have undergone extensive medical and genetic tests. Recipients may be up to 55 years of age.

## Preimplantation Genetic Diagnosis

Prenatal diagnostic tests such as amniocentesis, chorionic villus sampling, and fetal cell sorting can be used in pregnancies achieved with assisted reproductive technologies. A test called **preimplantation genetic diagnosis** (PGD) detects genetic and chromosomal abnormalities *before* pregnancy starts. The couple selects a very early “preimplantation” embryo. It is so-called because it would not normally have

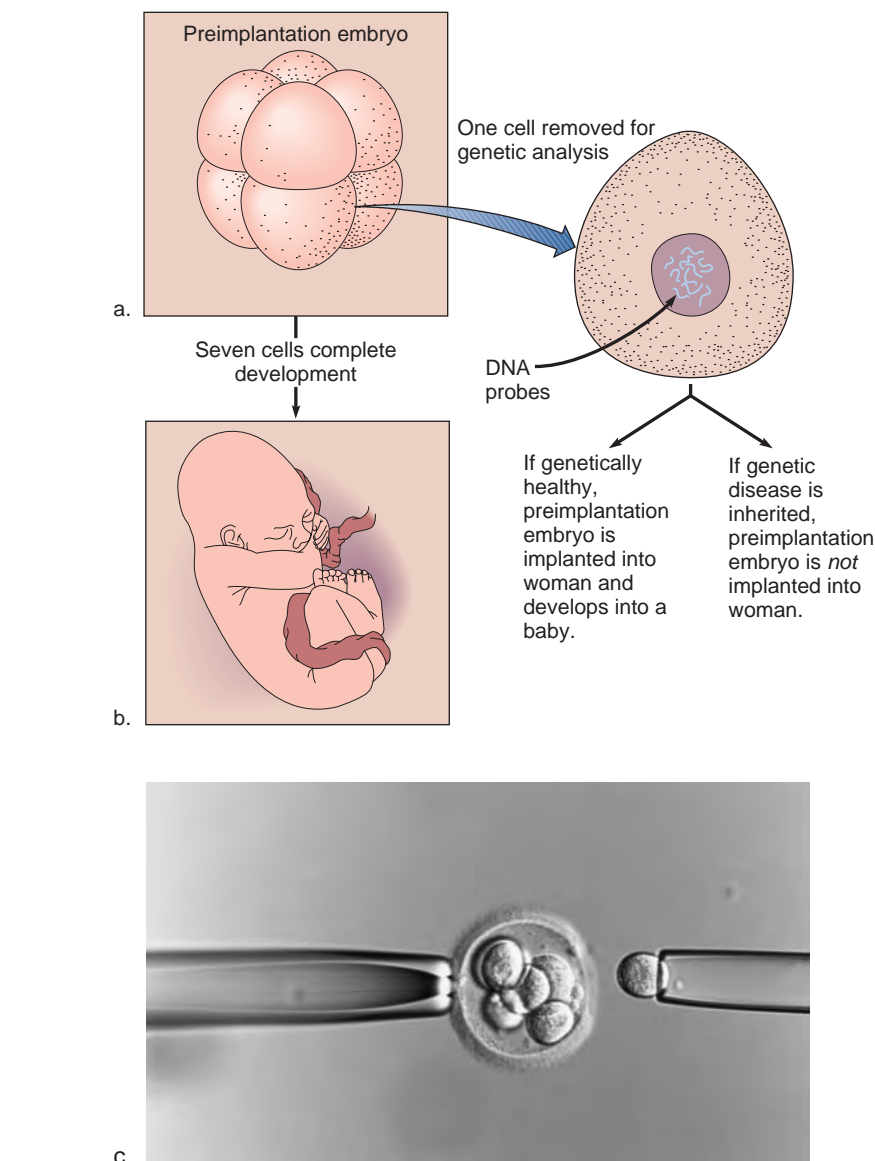
yet arrived at the uterus for implantation. The selected embryo has not inherited a specific detectable genetic condition. This was the technology used to select Adam Nash, whose umbilical cord stem cells cured his sister's Fanconi anemia (see figure 21.1). PGD has about a 29 percent success rate and does not increase the risk of birth defects.

PGD is possible because one cell, or blastomere, can be removed for testing from an 8-celled embryo and the remaining 7 cells can complete development normally in a uterus. Before the embryo is implanted into the woman the single cell is karyotyped, or its DNA amplified and probed for genes that the parents carry. Embryos that pass the chromosomal check-up are selected to complete development or are stored. At first, researchers implanted the remaining 7 cells, but letting the embryo continue developing in the dish until day 5, when it is 80 to 120 cells, is more successful. Obtaining the cell to be tested is called “blastomere biopsy” (figure 21.5). Accuracy is about 97 percent. Errors are generally due to mosaics—when a somatic mutation occurs in a blastomere—or during amplification of blastomere DNA. The tested cells in PGD can also be used to derive embryonic stem cells without destroying the 7-celled remainder.

The first children who had PGD were born in 1989. In these first cases, probes for Y chromosome-specific DNA sequences were used to select females, who could not inherit X-linked conditions their mothers carried. The alternative to PGD would have been to face the 25 percent chance of conceiving an affected male.

In March 1992, the first child was born who underwent PGD to avoid a specific inherited disease. Chloe O'Brien was checked as an 8-celled preimplantation embryo to see if she had escaped the cystic fibrosis that affected her brother. Since then, PGD has helped to select thousands of children free of several dozen types of inherited illnesses. It has been used for the better-known single-gene disorders as well as for many rare ones.

Today PGD is increasingly being used to screen early embryos derived from IVF for normal chromosome number before implanting them into women. This should increase the chances of successful



**Figure 21.5** Preimplantation genetic diagnosis (PGD) probes disease-causing genes or chromosome aberrations in an 8-celled preimplantation embryo. (a) A single cell is separated and tested to see if it contains a disease-causing genotype or chromosome abnormality. (b) If it doesn't, the remaining seven cells divide a few more times and are transferred to the oocyte donor to complete development. (c) This preimplantation embryo is held still by suction applied on the left. On the right, a pipette draws up a single blastomere. *In vitro* fertilization took place 45 hours previously.

live births, but in the first large trial, PGD actually lowered the birth rate—perhaps the intervention harms the embryos. For some couples, though, PGD and IVF work. One woman who had undergone several failed IVF attempts had five embryos checked. Four were abnormal, but with different chromosomes affected. The fifth embryo

became the couple's daughter. Obviously, one parent had very defective meiosis.

Like many technologies, preimplantation genetic diagnosis can introduce a bioethical “slippery slope” when it is used for reasons other than ensuring that a child is free of a certain disease, such as for gender selection. A couple with five sons might,

Table 21.3

## Some Assisted Reproductive Technologies

Technology	Procedures	Success/Cycle	Cost/Cycle
GIFT	Deposits collected oocytes and sperm in uterine tube.	27%	\$8,000–\$10,000
IVF	Mixes sperm and oocytes in a laboratory dish, with chemicals to simulate intrauterine environment to encourage fertilization.	29%	\$6,500–\$15,000
Intrauterine insemination	Places or injects washed sperm into the cervix or uterus.	5–25%	\$125
ICSI	Injects immature or rare sperm into oocyte, before IVF.	28%	\$10,000–\$17,000
Oocyte freezing	Oocytes retrieved and frozen in liquid nitrogen.	3%	\$8,000
Ovulation induction	Drugs control timing of ovulation in order to perform a particular procedure.	28%	\$3,000
PGD	Searches for specific mutant allele in sampled cell of 8-celled embryo. Its absence indicates remaining 7-celled embryo can be nurtured and implanted in woman, and child will be free of genetic condition.	29%	\$8,000–\$15,000
Surrogate mother	Woman carries a pregnancy for a woman who cannot become or stay pregnant.		\$10,000
ZIFT	Places IVF ovum in uterine tube.	29%	\$8,000–\$13,000

for example, use PGD to select a daughter. But this use of technology might just be a new expression of age-old human nature, according to one physician who performs PGD. “From the dawn of time, people have tried to control the sex of offspring, whether that means making love with one partner wearing army boots, or using a fluorescence-activated cell sorter to separate X- and Y-bearing sperm. PGD represents a quantum leap in that ability—all you have to do is read the X and Y chromosome paints,” he says.

While PGD used solely for family planning is certainly more civilized than placing baby girls outside the gates of ancient cities to perish, the American Society for Reproductive Medicine endorses the use of PGD for sex selection only to avoid passing on an X-linked disease. Yet even PGD to avoid disease can be controversial. In the United Kingdom, where the government regulates reproductive technology, inherited cancer susceptibility is an approved reason to have PGD. Three reasons that bioethicists cite to *not* use PGD for this reason are that these cancers do not begin until adulthood, the susceptibility is incompletely penetrant (not everyone who inherits the disease-associated genotype will actually develop cancer), and the cancer may be treatable or avoidable with surgery.

Table 21.3 summarizes the assisted reproductive technologies.

## Key Concepts

1. In intrauterine insemination, donor sperm are placed in a woman's reproductive tract.
2. A genetic and gestational surrogate mother is intrauterinely inseminated, becomes pregnant, then gives the baby to the father and his partner. A gestational surrogate mother gestates a baby conceived *in vitro* with gametes from a man and a woman who cannot carry a fetus.
3. In IVF, sperm and oocyte unite outside the body, and the resulting embryo is transferred to the uterus. Early embryos can also be frozen and used later.
4. In GIFT, sperm and oocytes are placed in a uterine tube at a site past a blockage.
5. In ZIFT, an IVF embryo is placed in a uterine tube.
6. In embryo adoption, a woman who has had intrauterine insemination has an early embryo washed out of her uterus and transferred to a woman who lacks oocytes.
7. PGD removes cells from early embryos and screens them for genetic or chromosomal abnormalities.

## 21.3 Extra Embryos

The overall success rates of assisted reproductive technologies are not spectacular in terms of live births, but at the early stages, ironically, they sometimes work too well. This leaves “extra” oocytes, fertilized ova, or very early embryos. Because human prenatal development cannot complete outside of a uterus, decisions must be made as to the fate of these biological materials. Clients of fertility facilities can either allow their oocytes, fertilized ova, or embryos to be stored indefinitely or discarded; donate them to other infertile couples; or donate them for use in research.

In the United States, nearly half a million embryos derived from IVF sit in freezers; some have been there for years. Most couples who donate embryos do so anonymously, with no intention of learning how their genetic offspring are raised. Scott and Glenda Lyons chose a different path when they learned that their attempt at IVF had yielded too many embryos.

In 2001, two of Glenda's 18 embryos were transferred to her uterus, and developed into twins Samantha and Mitchell. Through a website where couples chat about fertility issues, Scott and Glenda met and selected Bruce and Susan Lindeman to receive 14 remaining embryos. This second couple had tried IVF three times, with



no luck. The Lyons' frozen embryos were shipped cross-country to a clinic where two were implanted in Susan's uterus. In July 2003, Chase and Jack Lindeman were born—genetic siblings of Samantha and Mitchell Lyons. But there were still embryos left. The Lyons allowed the Lindemans to send twelve embryos to a third couple, who used two to have twin daughters in August 2004. They are biological siblings of Samantha and Mitchell Lyons and Chase and Jack Lindeman (figure 21.6).

Donating fertilized ova and embryos for use in research is another alternative to disposing of them. The results of these experiments sometimes challenge long-held ideas, indicating that we still have

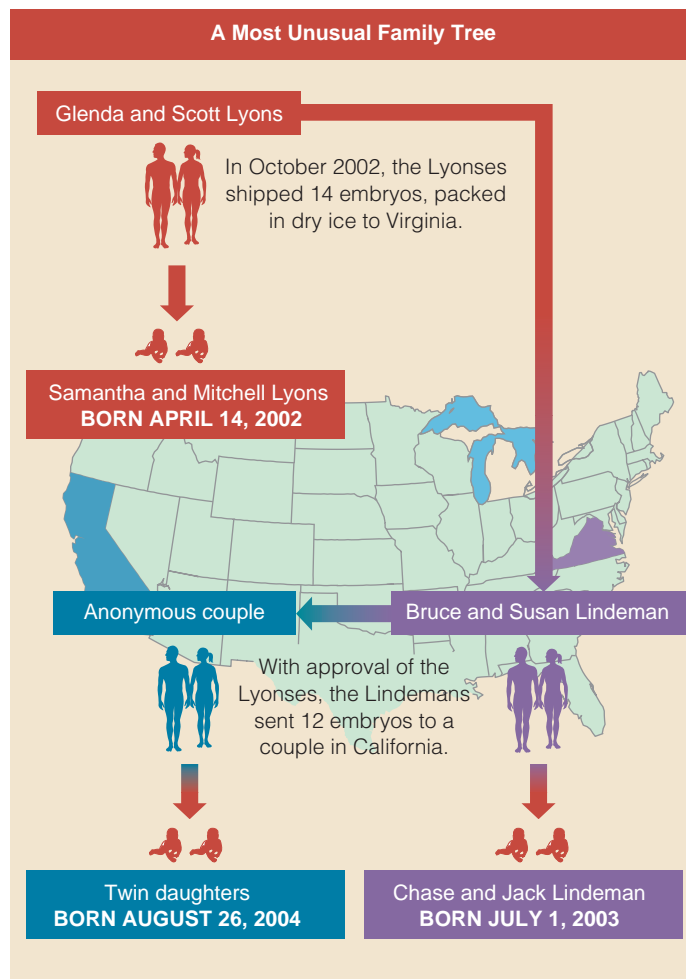
much to learn about early human prenatal development. This was the case for a study from Royal Victoria Hospital in Montreal. Researchers examined the chromosomes of sperm from a man with XXY syndrome. Many of the sperm would be expected to have an extra X chromosome, due to non-disjunction (see figure 13.12), which could lead to a preponderance of XXX and XXY offspring. Surprisingly, only 3.9 percent of the man's *sperm* had extra chromosomes, but five out of ten of his spare *embryos* had an abnormal X, Y, or chromosome 18. That is, even though most of the man's sperm were normal, his embryos weren't. The source of reproductive problems in XXY syndrome, therefore, might not be in the sperm, but in early embryos—a

finding that was previously unknown not expected, and was only learned because of observing embryos.

In another study, Australian researchers followed the fates of single blastomeres that had too many or too few chromosomes. They wanted to see whether the abnormal cells preferentially ended up in the inner cell mass, which develops into the embryo, or the trophectoderm, which becomes extra-embryonic membranes. The study showed that cells with extra or missing chromosomes become part of the inner cell mass much more frequently than expected by chance. This finding indicates that the ability of a blastomere sampled for PGD to predict health may depend on whether it is fated to be part of the inner cell mass.

Using fertilized ova or embryos designated for discard in research is controversial. Without regulations on privately funded research, ethically questionable experiments can happen. For example, researchers reported at a conference that they had mixed human cells from male embryos with cells from female embryos, to see if the normal male cells could “save” the female cells with a mutation. Sex was chosen as a marker because the Y chromosome is easy to detect. But the idea of human embryos with mixed sex parts caused a public outcry.

IVF is currently the major source of fertilized ova and early embryos for research. However this supply may diminish if an experimental ART becomes commonplace. **Polar body biopsy** is based on Mendel's first law, the segregation of alleles. In the technique, if a polar body resulting from the first meiotic division in a woman who is a carrier of an X-linked disorder has the mutant allele, then it is inferred that the oocyte to which it clings lacks that allele. Oocytes that pass this test can then be fertilized *in vitro* and the resulting embryo implanted in the woman. Polar body biopsy is possible because the polar body is attached to the much larger oocyte. A large pipette is used to hold the two cells in place, and a smaller pipette is used to separate the polar body. Then, DNA probes and FISH are used to look at genes and chromosomes in the polar body and infer the genotype of the oocyte (figure 21.7). Polar body



**Figure 21.6 Using extra embryos.** Six children resulted from Glenda and Scott Lyons' embryos. The Lyons had a boy and a girl, then donated embryos to the Lindemans, who had twin boys. Finally, a couple in California used the Lyons' embryos to have twin daughters. The Lyons and Lindemans have become friends.



**Figure 21.7 Polar body biopsy.**  
The fact that an oocyte shares a woman's divided genetic material with a much smaller polar body allows the screening of oocytes for use in IVF.

biopsy followed by PGD is quite effective in avoiding conceptions with chromosomal abnormalities or certain single-gene disorders. By adding this quality control, the ARTs can be more successful, but may decrease the supply of embryos for research.

ARTs introduce ownership issues (Table 21.4). Another controversy is that human genome information is providing more traits to track and perhaps control in coming generations. It is easy to envision routinely scanning the entire human genome in gametes, fertilized ova, or early

**Table 21.4**  
**Assisted Reproductive Disasters**

1. A physician in California used his own sperm to perform intrauterine insemination on 15 patients, telling them that he had used sperm from anonymous donors.
2. A plane crash killed the wealthy parents of two early embryos stored at  $-320^{\circ}\text{F}$  ( $-195^{\circ}\text{C}$ ) in a hospital in Melbourne, Australia. Adult children of the couple were asked to share their estate with two 8-celled siblings-to-be.
3. Several couples in Chicago planning to marry discovered that they were half-siblings. Their mothers had been inseminated with sperm from the same donor.
4. Two Rhode Island couples sued a fertility clinic for misplacing several embryos.
5. Several couples in California sued a fertility clinic for implanting their oocytes or embryos in other women without donor consent. One woman requested partial custody of the resulting children if her oocytes were taken, and full custody if her embryos were used, even though the children were of school age and she had never met them.
6. A man sued his ex-wife for possession of their frozen fertilized ova. He won, and donated them for research. She had wanted to be pregnant.
7. The night before *in vitro* fertilized embryos were to be implanted in a 40-year-old woman's uterus after she and her husband had spent four years trying to conceive, the man changed his mind, and wanted the embryos destroyed. Their embryo custody battle is before the Supreme Court.

embryos. Who will decide which traits are worth living with, and which aren't?

ARTs operate on molecules and cells, but with repercussions for individuals and families. Ultimately, if it becomes widespread enough, these interventions into reproduction may affect the gene pool. Let us hope that regulations will evolve along with the technologies to assure that they are applied sensibly and humanely.

## Key Concepts

1. IVF produces extra fertilized ova and early embryos that may be used, frozen, donated, or discarded.
2. Used in basic research, such embryos are adding to our knowledge of early human development.
3. Polar body biopsy enables physicians to identify and select out defective oocytes.

# Summary

## 21.1 Infertility and Subfertility

1. **Infertility** is the inability to conceive a child after a year of unprotected intercourse. Subfertile individuals or couples manufacture gametes, but take longer than usual to conceive. **Assisted reproductive technologies** replace what is missing in reproduction.
2. Causes of infertility in the male include low sperm count, a malfunctioning immune system, a varicose vein in the scrotum, structural sperm defects, drug exposure, vasectomy reversal, and abnormal hormone levels. In cases not associated with a physical problem, a mutation may impair fertility.

3. Female infertility can be caused by absent or irregular ovulation, blocked uterine tubes, an inhospitable or malshaped uterus, antisperm secretions, or lack of sperm-attracting biochemicals. Early pregnancy loss due to abnormal chromosome number is more common in older women and may appear to be infertility.

## 21.2 Assisted Reproductive Technologies

4. In **intrauterine insemination**, donor sperm are introduced into a woman's reproductive tract in a clinical setting.
5. A gestational and genetic surrogate mother provides her oocyte. Then intrauterine

insemination is performed with sperm from a man whose partner cannot conceive or carry a fetus. The surrogate also provides her uterus for nine months. A gestational surrogate mother receives an ***in vitro* fertilized** ovum that belongs genetically to the couple who ask her to carry it.

6. In IVF, oocytes and sperm meet in a dish, fertilized ova divide a few times, and the resulting embryos are placed in the woman's body, circumventing blocked tubes or the inability of the sperm to penetrate the oocyte. **Intracytoplasmic sperm injection** introduces immature or nonmotile sperm into oocytes.

7. Embryos can be frozen and thawed and then complete development when placed in a woman's uterus.
8. **GIFT** introduces oocytes and sperm into a uterine tube past a blockage; fertilization occurs in the woman's body. **ZIFT** places an early embryo in a uterine tube.
9. Oocytes can be frozen and stored. In embryo adoption, a woman undergoes intrauterine insemination. A week later, the embryo is washed out of her uterus and introduced into the reproductive tract of the woman whose partner donated the sperm.
10. Seven-celled embryos can develop normally if a blastomere is removed at the 8-cell stage and cleared for abnormal chromosomes or genes. This is **preimplantation genetic diagnosis**.
11. Extra fertilized ova and early embryos generated in IVF are used, donated to couples, stored, donated for research, or discarded. They enable researchers to study aspects of early human development that they could not investigate in other ways.
12. **Polar body biopsy** enables physicians to perform genetic tests on polar bodies and to infer the genotype of the accompanying oocyte.

### 21.3 Extra Embryos

11. Extra fertilized ova and early embryos generated in IVF are used, donated to

## Review Questions

1. Which assisted reproductive technologies might help the following couples? (More than one answer may fit some situations.)
  - a. A woman is born without a uterus, but manufactures healthy oocytes.
  - b. A man has cancer treatments that damage his sperm.
  - c. A woman undergoes a genetic test that reveals she will develop Huntington disease. She wants to have a child, but does not want to pass on this presently untreatable illness.
  - d. Two women wish to have and raise a child together.
  - e. A man and woman are each carriers of sickle cell disease. They do not want to have an affected child, but they also do not want to terminate a pregnancy.
  - f. A woman's uterine tubes are scarred and blocked, so an oocyte cannot reach the uterus.
  - g. A young woman must undergo abdominal radiation to treat ovarian cancer, but wishes to have a child.
2. Why are men typically tested for infertility before women?
3. A man reads his medical chart and discovers that the results of his sperm analysis indicate that 22 percent of his sperm are shaped abnormally. He wonders why the physician said he had normal fertility if so many sperm are abnormally shaped. Has the doctor made an error?
4. Cite a situation in which both man and woman contribute to subfertility.
5. How does ZIFT differ from GIFT? How does it differ from IVF?
6. A Tennessee lower court, in ruling on the fate of seven frozen embryos in a divorce case, called them "children *in vitro*." In what sense is this label incorrect?
7. Explain how preimplantation genetic diagnosis is similar to and different from CVS and amniocentesis, described in chapter 13.
8. What are some of the causes of infertility among older women?
9. How do each of the following assisted reproductive technologies deviate from the normal biological process?
  - a. *in vitro* fertilization
  - b. GIFT
  - c. embryo adoption
  - d. gestational-only surrogacy
  - e. intrauterine insemination
  - f. cytoplasmic donation
10. According to table 21.2, which ART has the highest success rate?
11. When Louise Joy Brown was born in 1978, many people were horrified and several government officials called for banning IVF. Today, more than a million people have been conceived using the technology. Are there any experimental treatments or technologies today that people are wary of that might one day become routine?
12. Explain how PGD works.

## Applied Questions

1. The San Antonio Embryo Bank is the first such facility in the United States. It offers IVF leftover embryos, which would otherwise remain in the deep freeze or be discarded, to people wanting to have children, for \$2,500 each. The bank circumvents bioethical concerns by claiming that it sells a service, not an embryo. People in favor of the bank claim that purchasing an embryo is not different from paying for sperm or eggs, or an adopted child. Those who object to the bank claim that it makes an embryo a commodity.
  - a. Do you think that an embryo bank is a good idea, or is it unethical?
  - b. Whose rights are involved in the operation of the embryo bank?
  - c. Who should be liable if a child that develops from the embryo has a medical problem?
  - d. Is the bank elitist because the cost is so high?
2. A newspaper columnist wrote that frozen human embryos are "microscopic Americans." President George W. Bush called them "unique and genetically complete, like every other human being." A stem cell researcher referred to embryonic stem cells as "like any other cell in an adult, no different from the skin cells you rub off with a towel after a shower."
  - a. What is your opinion of the status of an 8-celled human embryo?
  - b. What is your opinion of the status of a cell that descends from a cell removed from an 8-cell human embryo? Does the status depend upon the fate of the rest of the embryo?



- c. Do you think that there is any harm in an influential person, such as a journalist, politician, or researcher, stating the status of an embryo?
  - d. How might the following individuals respond to or feel about these definitions?
    - i. A woman who ended a pregnancy, for whatever reason
    - ii. A couple who have had a spontaneous abortion
    - iii. A stem cell researcher
    - iv. A person with a disease that one day may be treated with stem cells
    - v. A couple who have tried to conceive for a decade
3. At the same time that 62- and 63-year-old women gave birth, actors Tony Randall and Anthony Quinn became fathers at ages 77 and 78—and didn't receive nearly as much criticism as the women. Do you think this is an unfair double standard, or a fair criticism based on valid biological information?
  4. Many people spend thousands of dollars pursuing pregnancy. What is an alternative solution to their quest for parenthood?
  5. An Oregon man anonymously donated sperm that were used to conceive a child. The man later claimed, and won, rights to visit his child. Is this situation for the man more analogous to a genetic and gestational surrogate mother, or an oocyte donor who wishes to see the child she helped to bring into existence?
  6. Big Tom is a bull with valuable genetic traits. His sperm are used to conceive 1,000 calves. Mist, a dairy cow with exceptional milk output, has many oocytes removed, fertilized *in vitro*, and implanted into surrogate mothers. With their help, Mist becomes the genetic mother of 100 calves—far more than she could give birth to naturally. Which two reproductive technologies performed on humans are based on these two agricultural examples?
  7. State who the genetic parents are and who the gestational mother is in each of the following cases:
    - a. A man was exposed to unknown burning chemicals and received several vaccines during the first Gulf war, and abused drugs for several years before and after that. Now he wants to become a father, but he is concerned that past exposures to toxins have damaged his sperm. His wife undergoes intrauterine insemination with sperm from the husband's brother, who has led a calmer and healthier life.
    - b. A 26-year-old woman has her uterus removed because of cancer. However, her ovaries are intact and her oocytes are healthy. She has oocytes removed and fertilized *in vitro* with her husband's sperm. Two resulting embryos are implanted into the uterus of the woman's best friend.
    - c. Max and Tina had a child by IVF in 1986. At that time, they had three extra embryos frozen. Two are thawed years later and implanted into the uterus of Tina's sister, Karen. Karen's uterus is healthy, but she has ovarian cysts that often prevent her from ovulating.
    - d. Forty-year-old Christensen von Wormer wanted children, but not a partner. He donated sperm, which were used for intrauterine insemination of an Indiana mother of one. The woman carried the resulting fetus to term for a fee. On September 5, 1990, von Wormer held his newborn daughter, Kelsey, for the first time.
    - e. Two men who live together want to raise a child. They go to a fertility clinic, have their sperm collected and mixed, and used to inseminate a friend, who nine months later turns the baby over to them.
  8. Delaying childbirth until after age 35 is associated with certain physical risks, yet an older woman is often more mature and financially secure. Many women delay childbirth so that they can establish careers. Can you suggest societal changes, perhaps using a reproductive technology, that would allow women to more easily have children and careers?
  9. An IVF attempt yields 12 more embryos than the couple who conceived them can use. What could they do with the extras?
  10. What do you think children born of an assisted reproductive technology should be told about their origins?
  11. Wealthy couples could hire poor women as surrogates or oocyte donors simply because the adoptive mother does not want to be pregnant. Would you object to this practice? Why or why not?
  12. An IVF program in India offers preimplantation genetic diagnosis to help couples who already have a daughter to conceive a son. The reasoning is

that because having a male heir is of such great importance in this society, offering PGD can enable couples to avoid aborting second and subsequent female pregnancies. Do you agree or disagree that PGD should be used for sex selection in this sociological context?

## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study, chapter 21**, and **Web Activities** to find the website links needed to complete the following activities.

13. During the last Bush administration, the federal government banned research using human embryos, yet did not regulate the human reproductive technology field at all. What effect did this have on human stem cell research in the United States? Consult websites to learn what other nations have done in this research field.
14. Go to the Centers for Disease Control and Prevention website. Click on ART Trends, and use the information to answer the following questions.
  - a. Since 1996, to what extent has the use of ARTs in the U.S. increased?
  - b. Which is more successfully implanted into an infertile woman's uterus, a fresh or frozen donor oocyte?
  - c. Which is more successfully implanted into an infertile woman's uterus, a donated oocyte or one of her own?
  - d. What are two factors that could complicate data collection on ART success rates?
15. A company called Extend Fertility provides oocyte freezing services, telling women to "set your own biological clock." The home page states, "Today's women lead rich and busy lives—obtaining advanced degrees, pursuing successful careers, and taking better care of ourselves. As a result of this progress, many of us choose to have children later than our mothers did."
 

Look at the website. Discuss how it might be viewed by the following individuals:

  - a. A 73-year-old father of a healthy baby
  - b. A 26-year-old woman, married with no children but who wants them, facing six months of chemotherapy
  - c. An orphaned 10-year-old in Thailand
  - d. A healthy 28-year-old woman in the United States who wants to earn

degrees in medicine, law, and business before becoming pregnant

- e. A young mother in Mexico who is giving her son up for adoption because she cannot afford to raise him

### Case Studies and Research Reports

16. Doola is 32 years old and is trying to decide if she and her husband are ready for parenthood when she learns that her 48-year-old mother has Alzheimer disease. The mother's physician tells Doola that because of the early onset, the Alzheimer's could be inherited through a susceptibility gene. Doola is tested and indeed has the same dominant allele. She wants to have a child right away, so that she can enjoy many years as a mother. Her husband David feels that it wouldn't be fair to have a child knowing that Alzheimer disease likely lies in Doola's future.
  - a. Who do you agree with, and why?
  - b. David is also concerned that Doola could pass on her Alzheimer gene variant to a child. What technology might help them avoid this?
  - c. Is Doola correct in assuming that she is destined to develop Alzheimer disease?
17. Madeline is fertile, but her partner Cliff had his testicles removed to treat cancer when he was a teenager. He did not bank testicular tissue. To have a child that is genetically theirs, the couple wishes to

use a nucleus from one of Cliff's somatic cells, which would be transferred to an oocyte of Madeline's that has had its nucleus removed. The resulting cell would be cultured in the laboratory and then transferred to Madeline's uterus via standard IVF. Is the couple correct in assuming that the child would be genetically theirs? Cite a reason for your answer.

18. Natallie Evans had to have her ovaries removed at a young age because they were precancerous, so she and her partner had IVF and froze their embryos for use at a later time. Under British law, both partners must consent for the continued storage of frozen embryos. Evans and her partner split, and he revoked his consent. She sued for the right to use the embryos. She told the court, "I am pleased to have the opportunity to ask the court to save my embryos and let me use them to have the child I so desperately want."

What information should the court consider in deciding this case? Whose rights do you think should be paramount?
19. Colleen and Ellen were partners who had twin daughters using ART. Colleen was in her forties when they decided to have children, and she had large uterine fibroids, so she could not carry a pregnancy. They selected sperm from a sperm bank, which was used in intrauterine insemination on Ellen, but she did not conceive after several

attempts. Next Ellen tried IVF, to no avail. Finally, the women decided to combine their contributions. Colleen had oocytes collected and fertilized and implanted in Ellen's uterus. The women signed legal documents declaring Ellen the sole parent, with plans to consider a more shared arrangement five years later. At the clinic, Colleen signed a form that waived her rights to her oocytes or children resulting from their being fertilized. She would later claim that she signed it because she thought she had to for the procedure to be done. Ellen's name was recorded on the birth certificates of their twin daughters. Although both women were active parents, their relationship deteriorated, and when the girls were 6, Ellen moved them across the country and kept Colleen from visiting them. The case ended up in the courts, which ruled that Ellen is the mother. The Marin County Superior Court declared Colleen's relationship with the twins "legally irrelevant." Colleen has petitioned the Supreme Court of California to consider the case.

- a. Who is the genetic mother and who is the gestational mother?
- b. Do you agree with the Marin County Superior Court's decision that a genetic relationship is "legally irrelevant?"
- c. What information would you need to decide whether Colleen was being discriminated against because she is gay?

## A Second Look

1. What ART did Gaby V. have?
2. If Bruce's sperm had been nonmotile (unable to swim), what ART may have helped Gaby to conceive?
3. Freezing sperm shortly after death would probably not occur to most people. Under what circumstances do you think it is ethical for a woman to be inseminated with her deceased partner's sperm?

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*:

Charcot-Marie-Tooth disease  
Male infertility



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Genomics

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- 22.1 From Genetics To Genomics
- 22.2 The Human Genome Project and Beyond
  - DNA Sequencing
  - Many Goals
  - Technology Drives the Sequencing Effort
  - A Representative One Percent
- 22.3 Comparative Genomics
- 22.4 Do You Want Your Genome Sequenced?

## AN ALGA HELPS EXPLAIN A HUMAN DISEASE

Researchers are comparing genome information from an ever-expanding list of species. While revealing much about evolution, comparative genomics can also illuminate human disease. This is the case for the very rare Bardet-Biedl syndrome (BBS, OMIM 209900).

BBS causes learning disabilities, obesity, blindness, extra digits, and kidney problems. Causative genes have been linked to eight chromosomes. In 2003, researchers implicated impaired cilia, the structures that fringe certain cells. Cilia wave, moving secretions across cell surfaces and moving the cells themselves, and they pick up signals. Abnormal or missing cilia can cause a variety of symptoms because so many cell types are affected. For example, early in embryonic development, waving cilia control how cells move to form tissues. When cilia do not form properly, organs may develop on the wrong side of the body! Cilia grow from structures called basal bodies.

To identify the genes behind BBS, researchers sought clues in genomes, focusing on a single-celled green alga that has basal bodies, humans, and a small plant in the mustard family whose cells lack basal bodies. The alga and humans share 4,348 genes, 3,660 of which are also in the plant genome. Subtracting the 3,660 genes that could not be involved in cilia formation left 688 genes. Researchers who work with BBS families consulted linkage data that pointed to 230 genes on part of human chromosome 2 as possible cilia genes. Only 2 of these 230 human genes were also in the alga, and one of these causes BBS. Researchers now have to discover how abnormal cilia cause symptoms.



The genome of the ciliated green alga *Chlamydomonas reinhardtii* held clues to a disease of humans.



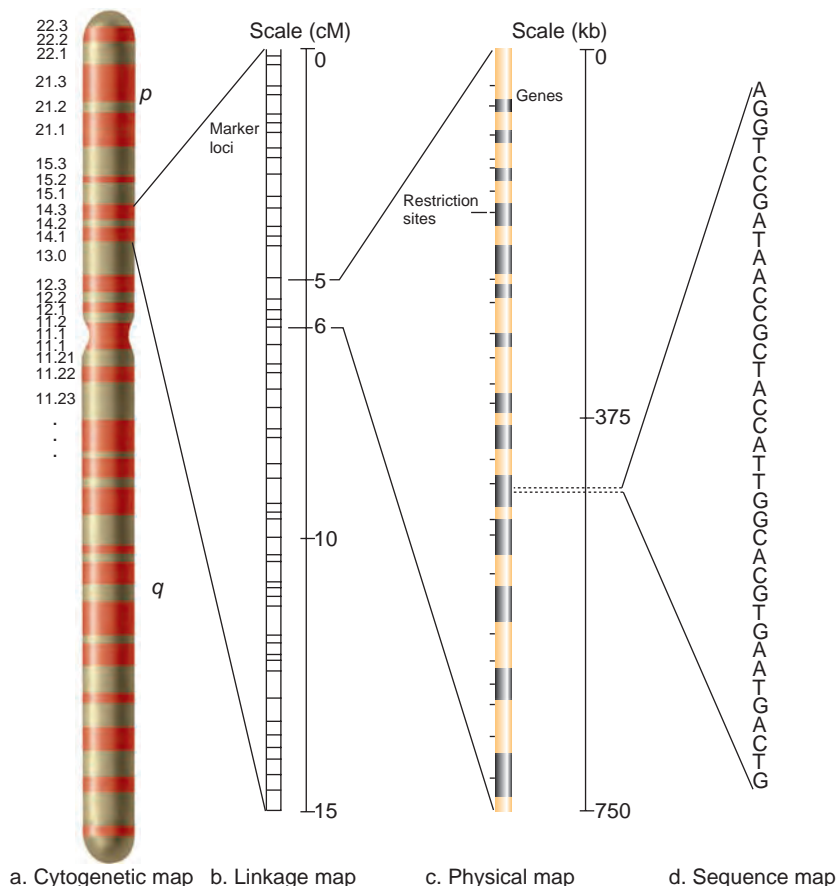
Genetics is a young science, genomics younger still. As one field has evolved into another, milestones have come at oddly regular intervals. A century after Gregor Mendel announced and published his findings, the genetic code was deciphered; a century after his laws were rediscovered, the human genome was sequenced. Today it is clear that knowing the genome sequence is only a start. Many milestones are yet to come.

## 22.1 From Genetics To Genomics

A genome is like a book, written in a four-letter alphabet arranged into gene-words that form an instruction manual for an individual, and on a broader scale, for a species. The term *genome* was coined in 1920 by geneticist H. Winkler. A hybrid of “gene” and “chromosome,” genome denotes a complete set of chromosomes and its genes. The modern definition refers to all the DNA in a haploid set of chromosomes, including non-protein-encoding sequences. The term *genomics*, credited to T. H. Roderick in 1986, indicates the study of genomes. Thoughts of genomes in general, and of the human genome in particular, lay in the background through much of the twentieth century, as researchers defined and described the units of inheritance from various perspectives.

The human genome was sequenced in the 1990s. It began with deciphering signposts and developing shortcuts. Many of the initial steps and tools grew from existing technology. Linkage maps from the 1950s on and many family studies that associated chromosomal aberrations with syndromes enabled researchers to assign some genes to their chromosomes. Then automated DNA sequencing took genetic analysis to a new level—information. **Figure 22.1** schematically illustrates the refinement and increasing resolution of different types of genetic maps.

The evolution of increasingly detailed genetic maps is similar to zooming in on a geographical satellite map. A cytogenetic map is like a map of California within a map of the United States, highlighting only the largest cities. A linkage map is like a map that depicts the smaller cities and large towns, and a physical map is similar to a geographical map indicating all towns. Finally, a sequence map is the equivalent



**Figure 22.1** Different levels of genetic maps are like zooming up the magnification on a geographical map. (a) A cytogenetic map, based on associations between chromosome aberrations and syndromes, can distinguish DNA sequences that are at least 5,000 kilobases (kb) apart. (b) A linkage map derived from recombination data distinguishes genes hundreds of kb apart. (c) A physical map constructed from overlapped DNA pieces distinguishes genes tens of kb apart. (d) A sequence map depicts the order of nucleotide bases.

of a finely detailed street map of part of a town or city, showing every building. All but sequence maps are now largely obsolete. Like Mapquest replacing the use of printed maps to plan a trip, finding specific sequences in databases is much faster than the older approaches.

Before and during the human genome project, many researchers matched single genes to specific diseases using an approach called **positional cloning**. The technique began with examining a particular phenotype corresponding to a Mendelian disorder in large families, then identifying parts of the genome that only affected relatives shared. Such sequences could serve as “markers” of the presumably tightly linked disease-causing gene. Instead of directly comparing DNA sequences, researchers compared sequences indirectly

by determining the effect of single base differences (SNPs) on the sizes of DNA pieces (RFLPs) that result from using DNA cutting enzymes, discussed in section 14.4.

In the 1980s and 1990s, positional cloning experiments yielded a steady stream of discoveries of genes that cause such diseases as Duchenne muscular dystrophy, cystic fibrosis, and Huntington disease (Reading 22.1, page 431). It took years to find a single gene. Today, using the human genome sequence and tools to analyze it, many a graduate student has found a disease-causing gene in just weeks.

Genomics has changed how we look at gene discovery, which has become a largely informational science. Researchers routinely mine genome databases for DNA sequence similarities. Each time a new species has its genome sequenced,



## Reading 22.1

# Discovering the Huntington Disease Gene

The story of the discovery of a marker for Huntington disease (HD) illustrates the gene-by-gene approach of research that immediately preceded the human genome project. The Bioethics Box in chapter 4 describes this autosomal dominant neurodegenerative disorder. The HD gene is near the tip of the short arm of chromosome 4 and encodes a protein, huntingtin, that is synthesized in the brain. The mutation is an expanded triplet repeat that adds glutamines to the protein. In certain brain cells, the added material disrupts folding of huntingtin, interfering with its interactions with other proteins (see table 10.6).

The search for the HD gene began with a large family in a remote village on the shores of Lake Maracaibo, Venezuela. Seven generations ago, in the 1800s, a local woman married a visiting Portuguese sailor or who, according to folklore, walked as if intoxicated. Like many couples in the poor fishing village, the woman and her sailor had many children. Some grew up to walk in the same peculiar way as their father. Of their nearly 5,000 descendants, more than 250 living today have HD. This extended family presented a natural experiment to geneticists, and they began their quest for a marker by drafting a huge pedigree that eventually depicted more than 10,000 individuals and stretched to more than 100 feet in width (**figure 1**) The Venezuela family was large enough to detect a marker-disease gene association. Studies at the DNA and chromosomal levels followed.

In 1981, Columbia University psychologist Nancy Wexler, whose mother would eventually die of HD, began annual visits to Lake Maracaibo. The people lived in huts perched on stilts, as their ancestors did. Wexler traded candy and blue jeans for blood samples and skin biopsies to bring back to a team of geneticists. Meanwhile, investigators at Massachusetts General Hospital were sampling tissue from an Iowa family of 41, in which 21 individuals had HD. They extracted DNA from the samples, cut it with restriction enzymes, and tested the fragments with a set of labeled DNA



**Figure 1** Nancy Wexler consults the enormous Venezuelan HD pedigree.

probes. They were looking for a probe that bound only the DNA of sick people. This would reveal a RFLP (see section 14.4) unique to people with the disease. The team added the Venezuelan DNA. A group at Indiana University matched the probe data to pedigrees, seeking a pattern.

With several hundred DNA probes and samples, the researchers expected the testing to take a long time, but luck was on their side. On a warm May night in 1983, the twelfth probe tested, called G8, matched. In both families it bound only the DNA of the sick people. G8 was linked to, and inherited with, the HD gene. Until the gene itself was discovered in 1993, this marker was the basis of presymptomatic testing.

The next step was to localize G8 to a chromosome. The researchers used hybrid rodent/human cells that contain only one human chromosome each. The hybrid cell that included G8 had human chromosome 4. To extend the DNA sequence from the marker to the HD gene, the researchers located another probe that overlapped the first, then another probe that overlapped the second probe, and so on. This technique was called “chromosome walking.” Finally, a computer aligned the probes according to their sequence

overlaps, creating a map of the extended DNA sequence.

The area surrounding a probe on a chromosome can harbor many genes. Researchers first narrowed down possible protein-encoding regions by looking for stretches of CGCGCG called “CpG islands,” which precede genes. That analysis showed that the half-million-base-long map could include 100 genes! Which were “candidate genes” for HD? The investigators needed another clue, related to the phenotype. The researcher who had discovered that an expanding triplet repeat causes myotonic dystrophy (see figure 12.10) suggested that perhaps this type of mutation lay behind HD, too, since both disorders affect movement.

Looking for a triplet repeat was a long shot, but the researchers found it—a 210,000-base stretch of DNA in people who do not have HD is considerably longer in those who do. Next, the researchers looked for gene expression in cDNA libraries made from various differentiated cells (see figure 19.6). The expanding gene was indeed in brain cDNA libraries. It was the HD gene. Marker tests, which could only be done in certain families amid much uncertainty, were soon replaced with direct mutation tests, which any person can take.



researchers can consult those done earlier and identify gene functions to fill in blanks in the story of evolution. The overall focus has shifted from identifying single genes to considering hierarchies of multigene function and interactions.

### Key Concepts

- 1. Human genome sequencing was built on linkage and cytogenetic information from decades of work.
- 2. Positional cloning located specific disease-causing genes in families.
- 3. Attention has shifted to understanding hierarchies of gene function.

## 22.2 The Human Genome Project and Beyond

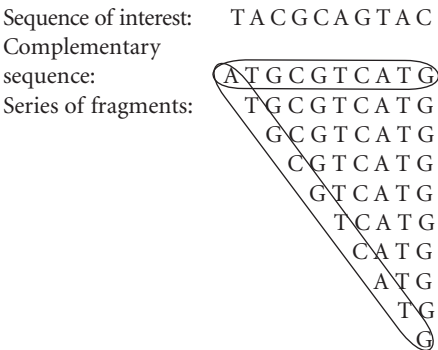
The idea of sequencing an entire genome probably occurred to many researchers as soon as Watson and Crick determined the structure of DNA. In 1966, Francis Crick proposed sequencing all genes in *E. coli* to reveal how the organism works, writing that “this particular problem will keep very many scientists busy for a long time to come.” Jacques Monod, who described the first genetic control system in bacteria, wrote at about the same time, “What is true for *Escherichia coli* is true for the elephant,” meaning that to know genomes is to understand all life. It was a gross oversimplification.

For sequencing genomes to evolve from science fiction to science required the development of key tools and technologies (see the Technology Timeline). First was the need to obtain the nucleotide base sequence of pieces of DNA. Then, computer programs would have to align and detect sequence overlaps in pieces cut from multiple copies of a genome, and assemble them to reconstruct each chromosome.

### DNA Sequencing

Several new ways to sequence DNA are available today, but one of the original methods, invented in 1977 by Frederick Sanger, is still widely used and was quite brilliant in concept. The Sanger method generates a series of DNA fragments of

identical sequence that are complementary to the DNA sequence of interest. These fragments differ in length from each other by one end base, as follows:



Note that the entire complementary sequence appears in the sequence of end

bases of each fragment. The complement of the gene of interest is cut into a collection of pieces, differing in the end bases, which are distinguished with a radioactive or fluorescent label. Then the fragments are separated by size. Once the areas of overlap are aligned, reading the labeled end bases of the pieces in size order reveals the sequence of the complement. Replacing A with T, G with C, T with A, and C with G establishes the sequence of interest. **Figure 22.2** shows how DNA sequence data derived from the Sanger method appear in scientific papers, and **figure 22.3** shows how the sequence is read from the end bases.

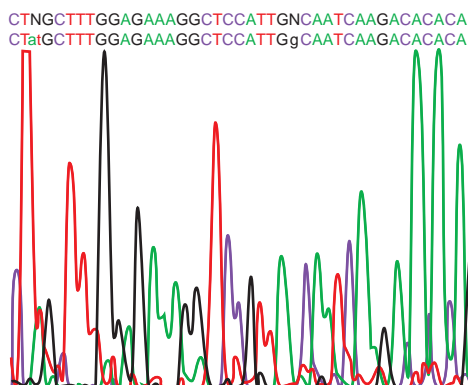
Newer approaches to DNA sequencing use a microfluidics environment, which

## Technology Timeline

### Evolution of the Human Genome Project

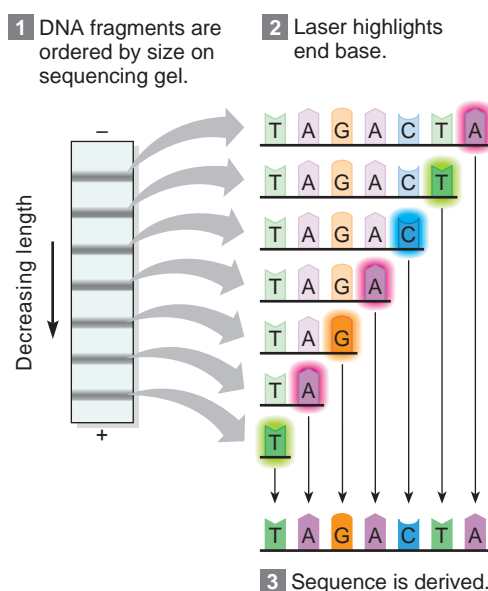
1985–1988	Idea to sequence human genome suggested at several scientific meetings.
1988	Congress authorizes the Department of Energy and the National Institutes of Health to fund the human genome project.
1989	Researchers at Stanford and Duke Universities invent DNA microarrays.
1990	Human genome project officially begins.
1991	Expressed sequence tag (EST) technology identifies protein-encoding sequences.
1992	First DNA microarrays available.
1993	Need to automate DNA sequencing recognized.
1994	U.S. and French researchers publish preliminary map of 6,000 genetic markers, one every 1 million bases along the chromosomes.
1995	Emphasis shifts from gene mapping to sequencing.
1996	Resolution to make all data public and updated daily at GenBank website.
1998	Public Consortium releases preliminary map of pieces covering 98 percent of human genome. Millions of sequences listed in GenBank. Directions for developing DNA microarrays posted on the Internet.
1999	Rate of filing of new sequences in GenBank triples. Public Consortium and two private companies race to complete sequencing.
2000	Microarray technology flourishes.
2001	Two versions of human genome sequence published.
2003	Finished version of human genome sequence announced to coincide with fiftieth anniversary of discovery of DNA structure. Entire protein-encoding part of human genome available on DNA microarrays.
2005	Annotation of human genome sequence continues gradually. Number of species with sequenced genomes soars.
2007 and beyond	Detailed analysis of a representative one percent of the human genome confirms that many genes have introns and reveals that most of the genome is transcribed.





**Figure 22.2 DNA sequence data.**

In automated DNA sequencing, a readout of sequenced DNA is a series of wavelengths that represent the terminal DNA base labeled with a fluorescent molecule.



**Figure 22.3 Reading a DNA sequence.**

A computer algorithm detects and records the end base from a series of size-ordered DNA fragments.

is a small, fluid-filled chamber. One technique sequences many 100-base-long single-stranded DNA pieces that are on tiny beads in a water-oil mixture. A laser reads off fluorescently tagged bases that are added, according to the complementary base pair rules, as nucleotides stream past the strands. The method, called 454 sequencing, was invented by a father seeking a way to quickly sequence his newborn son's genome. The technique can sequence 20 million bases in about four and a half hours.

## Many Goals

The human genome was sequenced for several reasons. The idea originated at a meeting held by the Department of Energy (DOE) in 1984 to discuss the long-term population genetic effects of exposure to low-level radiation. In 1985, researchers meeting at the University of California, Santa Cruz, called for an institute to sequence the human genome, because sequencing of viral genomes had shown that it could be done. The next year, virologist Renato Dulbecco proposed that the key to understanding the origin of cancer lay in knowing the human genome sequence. Later that year, scientists convened at the Cold Spring Harbor Laboratory on New York's Long Island for a meeting on "The Molecular Biology of *Homo Sapiens*" and discussed the feasibility of a human genome project. Attendees packed the room, and at first those against the project outnumbered those for it 5 to 1. The major fear was the shifting of goals of life science research from inquiry-based experimentation to amassing huge amounts of data.

A furious debate ensued, with detractors claiming that the project would be more gruntwork than a creative intellectual endeavor, comparing it to conquering Mt. Everest just because it is there. Practical benefits would be very far in the future. Some researchers feared that such an unprecedented "big science" project would divert government funds from basic research and AIDS. People even objected to sequencing "all the stuff between genes and within introns," as one attendee noted. The non-protein-encoding portion of the genome was then considered to be "junk," simply because we did not know what it did. Finally, the National Academy of Sciences convened a committee representing both sides to debate the feasibility, risks, and benefits of the project. The naysayers were swayed to the other side. So in 1988, Congress authorized the National Institutes of Health (NIH) and the DOE to fund the \$3 billion, 15-year human genome project.

The government-sponsored human genome project officially began in 1990 with James Watson at the helm. Recognizing the profound effect that genetic information would have on public policy and on peoples' lives, the project set aside 3 percent of its budget for the ELSI program, which

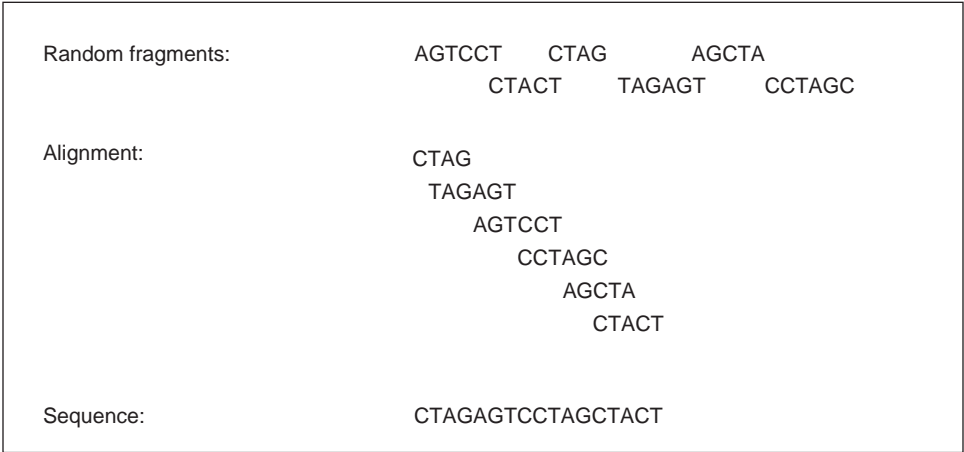
stands for ethical, legal, and social issues. ELSI helps ensure that genetic information is not misused to discriminate against people with particular genotypes.

The human genome project expanded in scope and participants. In addition to ten major sequencing centers, the largest in England, France, Germany, and Japan, many hundreds of other research laboratories and biotechnology companies contributed DNA sequence data. The goal was eventually accomplished by an international consortium and a private company, Celera Genomics. In addition to sequencing the human genome, the public project also planned to sequence the genomes of several model organisms.

## Technology Drives the Sequencing Effort

The fifteen-year timetable for the human genome project was conservative. It assumed that methods to speed DNA sequencing would be invented along the way. This is indeed what happened. In 1991, for example, a shortcut called expressed sequence tag (EST) technology enabled researchers to quickly pick out genes most likely to be implicated in disease. ESTs are cDNAs (see figure 19.6) made from the mRNAs in a cell type that is abnormal in a particular illness. Also in that year, DNA microarrays were developed to display cDNAs. Microarray technology has proved to perhaps be even more important than sequencing the genome because it displays gene expression, which can reflect gene interactions—important information not revealed in the sequence alone.

Sequencing and mapping improved greatly from 1993 to 1998. At the start, researchers cut the genome into overlapping pieces of about 40,000 bases (40 kilobases), then randomly cut the pieces into small fragments. Researchers would cut several genomes in a single experiment, so that many resulting fragments overlapped. By finding the overlaps, the pieces could be assembled to reveal the overall sequence. The greater the number of overlaps, the more complete the final assembled sequence. It was also important that the sites of overlap be unique sequences, found in only one place in the genome. Overlaps of repeated sequences found in several places in the genome could lead to more than one



**Figure 22.4 Deriving a DNA sequence.** Automated DNA sequencers first determine the sequences of short pieces of DNA, or sometimes of just the ends of short pieces. Then algorithms search for overlaps. By overlapping the pieces, the software derives the overall DNA sequence.

derived overall sequence—a little like searching a document for the word “that” versus searching for an unusual word, such as “dandelion.” Searching for “dandelion” is more likely to lead to a specific part of a document, whereas “that” may occur in several places—just like repeats in a genome. The Y chromosome, with its many repeats, was extremely difficult to sequence, and had to be cut into very small pieces. Another problem was to determine which side of the double helix to sequence for each piece. **Figure 22.4** depicts how a DNA sequence might be reconstructed from overlapping pieces.

The human genome project examined thousands of pieces of DNA at a time. The sequences were cataloged continually in a public database called GenBank, and at some companies. Two general approaches tackled the many pieces of DNA (**figure 22.5**). The “clone-by-clone” technique aligned pieces one chromosome at a time. The “whole genome shotgun” approach shattered the entire genome, then used a computer algorithm to identify overlaps and align them to derive a continual sequence. The task can be compared to cutting the binding off a large book, throwing it into the air, and reassembling the dispersed pages in order. A “clone-by-clone” dismantling of the book would divide it into bound chapters. The whole genome shotgun approach would free every page. Whole genome shotgunning is faster, but it misses some sections (particularly repeats) that the clone-by-clone method detects, and it does not work well on large genomes.

Technical advances continued. In 1995, DNA sequencing became automated, and software was developed that could rapidly locate the unique sequence overlaps among many small pieces of DNA and assemble them into a continuous sequence, eliminating the preliminary step of gathering large guidepost pieces. This software enabled researchers at The Institute for Genomic Research (TIGR), a private research institute, to sequence the first complete genome for an organism in under a year. It was *Haemophilus influenzae*, a bacterium that causes meningitis and ear infections. The researchers cut the bacterium’s 1,830,137 bases into 24,000 fragments and sequenced them, and the software assembled the overlaps of several genomes’ worth of pieces. The human genome is 1,500 times larger than that of *H. influenzae*.

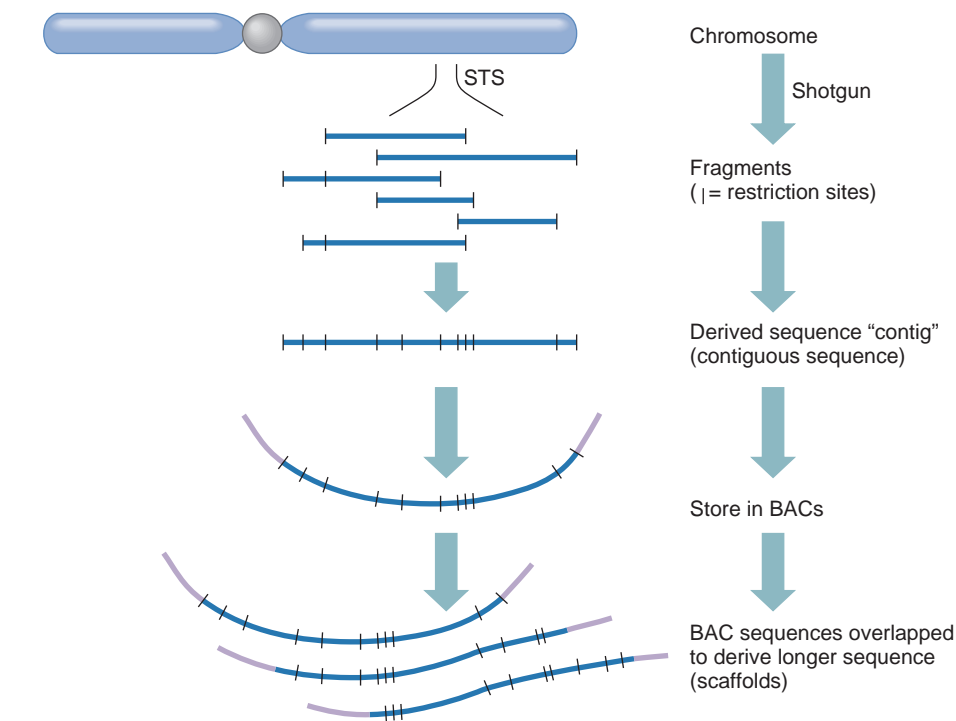
In 1999, the human genome project became intensely competitive between the

Table 22.1	
Steps in Genome Sequencing and Analysis	
1.	Obtain chromosome maps with landmarks from classical linkage or cytogenetic studies, or RFLP sites.
2.	Obtain chromosome pieces maintained in gene libraries, or shotgun entire sequence.
3.	Sequence the pieces.
4.	Overlap aligned sequences to extend the known sequence.
5.	Compare the sequence to those in other species.
6.	Annotate the sequence (identify genes and assign functions).
7.	Study gene expression and gene interactions.

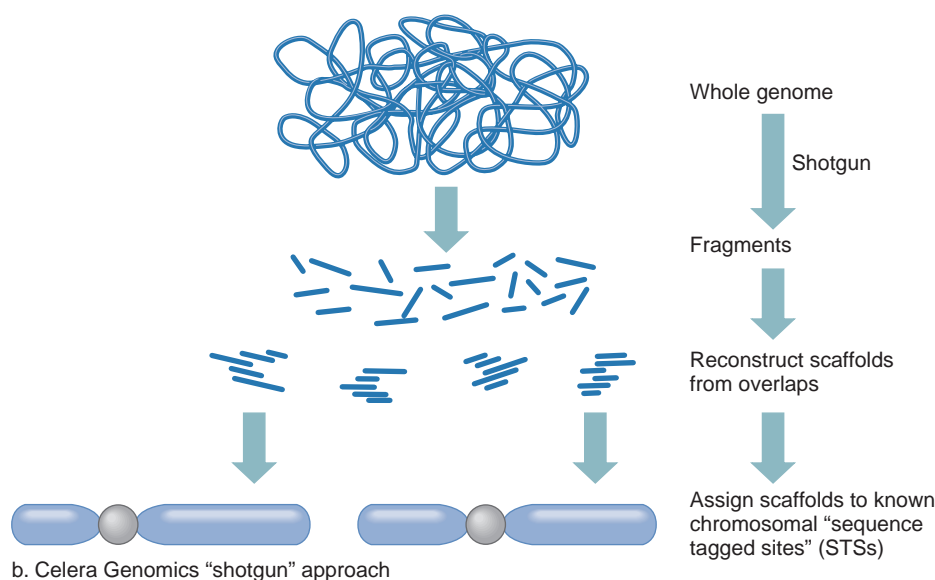
public and private efforts. In the end, the battling factions called a truce. On June 26, 2000, Craig Venter from Celera Genomics and Francis Collins, representing the public international consortium, flanked President Clinton in the White House rose garden to unveil the “first draft” of the human genome sequence. The milestone capped a decade-long project involving thousands of researchers, which in turn was the culmination of a century of discovery. The historic June 26 date came about because it was the only opening in the White House calendar! In other words, the work was monumental; its announcement, staged.

**Figure 22.6** is an overview of genome sequencing and one application—gene expression profiling using DNA microarrays, discussed in chapter 11. **Table 22.1** summarizes steps in genome sequencing and **table 22.2** lists websites that have genome sequence information.

Table 22.2	
Public Genome Databases	
Organization	Website
GenBank	<a href="http://www.ncbi.nlm.nih.gov/Genbank/">http://www.ncbi.nlm.nih.gov/Genbank/</a>
European Molecular Biology Laboratory (EMBL)	<a href="http://www.ebi.ac.uk/embl/index.html">www.ebi.ac.uk/embl/index.html</a>
DNA Data Bank of Japan	<a href="http://www.ddbj.nig.ac.jp">www.ddbj.nig.ac.jp</a>
University of California, Santa Cruz	<a href="http://www.genome.ucsc.edu/">www.genome.ucsc.edu/</a>
Genome Browser	
National Center for Biotechnology Information Map Viewer	<a href="http://www.ncbi.nlm.nih.gov/mapview/">www.ncbi.nlm.nih.gov/mapview/</a>
National Human Genome Research Institute, NIH	<a href="http://www.genome.gov/">www.genome.gov/</a>
U.S. Department of Energy Genomes to Life	<a href="http://genomicsgtl.energy.gov/">http://genomicsgtl.energy.gov/</a>
Genomes OnLine Database (GOLD)	<a href="http://www.genomesonline.org/">http://www.genomesonline.org/</a>



a. International Human Genome Mapping Consortium "BAC by BAC"  
(BAC = bacterial artificial chromosome)



b. Celera Genomics "shotgun" approach

**Figure 22.5 Two routes to the human genome sequence.** (a) The International Consortium began with known chromosomal sites and overlapped large pieces, called contigs, that in turn were reconstructed from many small, overlapping pieces. "STS" stands for "sequence tagged site," which refers to specific known parts of chromosomes. A BAC is a cloning vector that uses bacterial DNA (see Table 19.2). (b) Celera Genomics shotgunned several copies of a genome into small pieces, overlapped them to form scaffolds, and then assigned scaffolds to known chromosomal sites. They used some Consortium data.

## A Representative One Percent

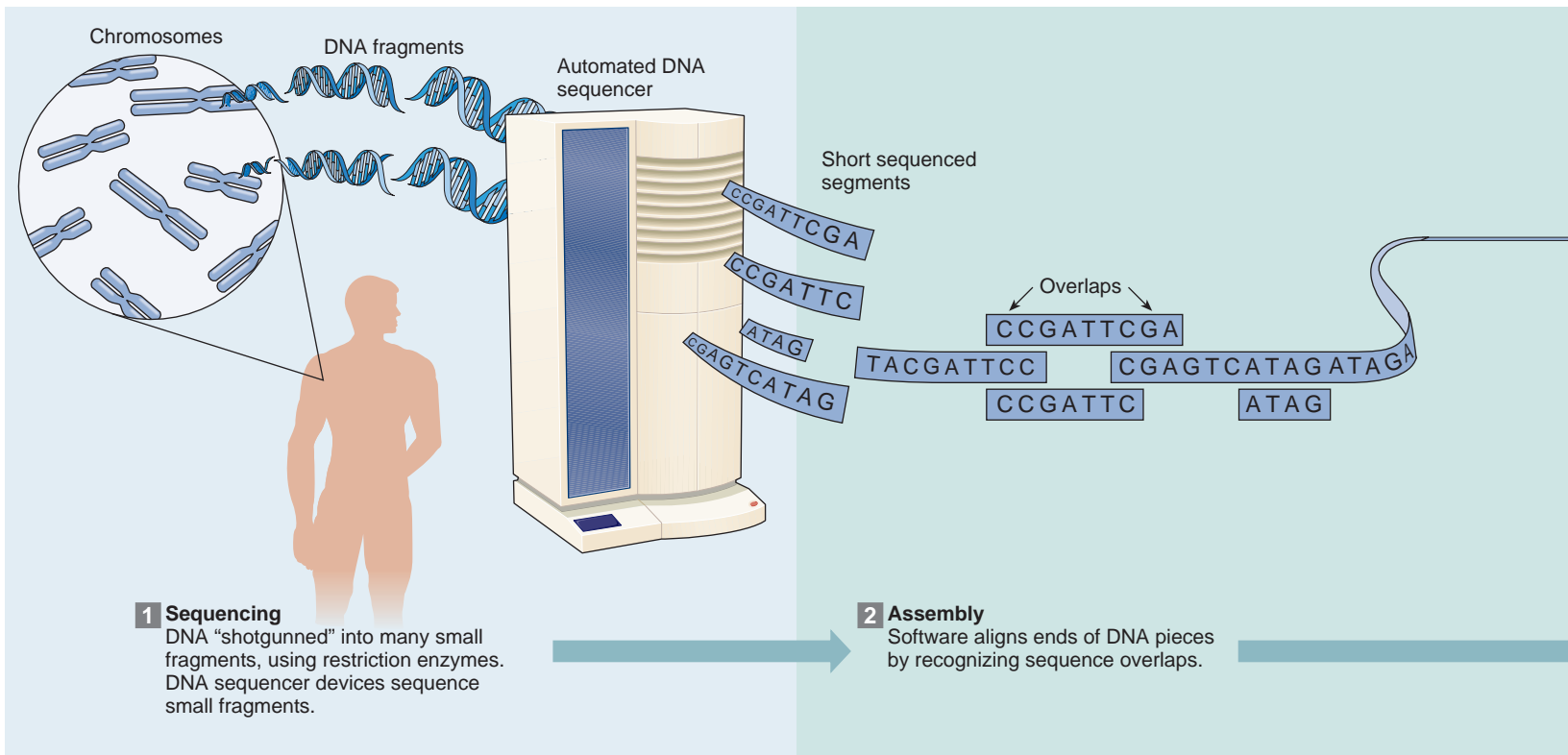
Sequencing a genome is a first step. Next comes annotation, which is the assigning of functions (such as encoding a specific protein) to particular sequences. Once annotation of the human genome was underway, analysis moved to a more global level—looking at large-scale genome architecture, and how the various elements of a genome interact.

To accomplish this broader view of how a genome works, an international group of researchers scrutinized a representative one percent of the genome. The coverage, spread among the chromosomes, amounted to 30 million of our 3 billion DNA bases. The DNA sequences came from known, well-studied genes as well as uncharted territory, with an initial goal of deriving a "parts list" of that one percent. The project, called ENCODE (Encyclopedia of DNA Elements), began work in 2003 and published first results in 2007.

The ENCODE project is filling in the gaps between the single-gene protein-encoding approach that dominated genetics for decades and evolutionary clues from comparing the genomes of many species, discussed in the next section. So far, results have confirmed and extended a complexity that researchers had begun to suspect with the discovery of introns in the late 1970s. *The old view:* The human genome is a static collection of individual protein-encoding genes, acting alone, mired in a sea of "junk" sequences. *The new view:* Most, if not all, of the human genome consists of classes of DNA that have different types of functions that interact through space and time to control cellular activities. The human genome functions more like hypertext than individual units of information.

As with many aspects of our lives, genetics has turned out to be not nearly as simple as we thought. **Table 22.3** highlights preliminary findings of the ENCODE project.





**Figure 22.6 Sequencing genomes.** Determining the DNA sequence of a genome is just a first step—albeit a huge one. After pieces are assembled, protein-encoding genes are identified, and then patterns of gene expression in different tissues are assessed.

## Key Concepts

1. DNA sequencing and computer software to align DNA pieces were essential for genome projects to proceed.
2. In the Sanger method of DNA sequencing, complementary copies of an unknown DNA sequence are cut into different-sized pieces differing from each other by an end base. The pieces are overlapped by size and the labeled end bases read off.
3. The idea to sequence the human genome emerged in the mid-1980s with several goals. The project officially began in 1990.
4. Genome sequencing cuts several copies of a genome, sequences the pieces, then uses algorithms to overlap the pieces and derive sequence.
5. Clone-by-clone sequencing assembles chromosomes individually. Whole genome shotgun sequencing shatters the entire genome and rebuilds it.
6. The ENCODE project is taking an in-depth look at one percent of the human genome.

**Table 22.3**

### ENCODE Results

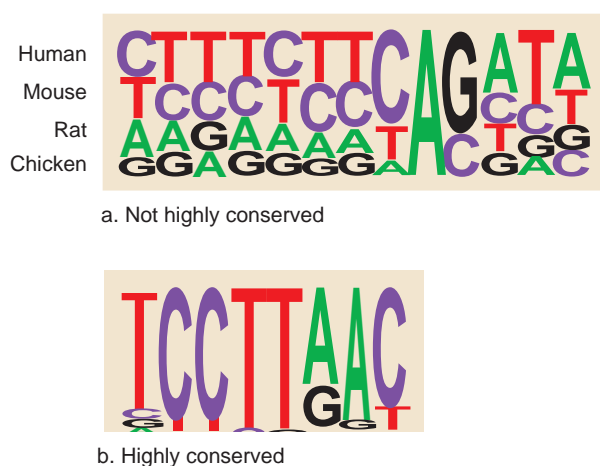
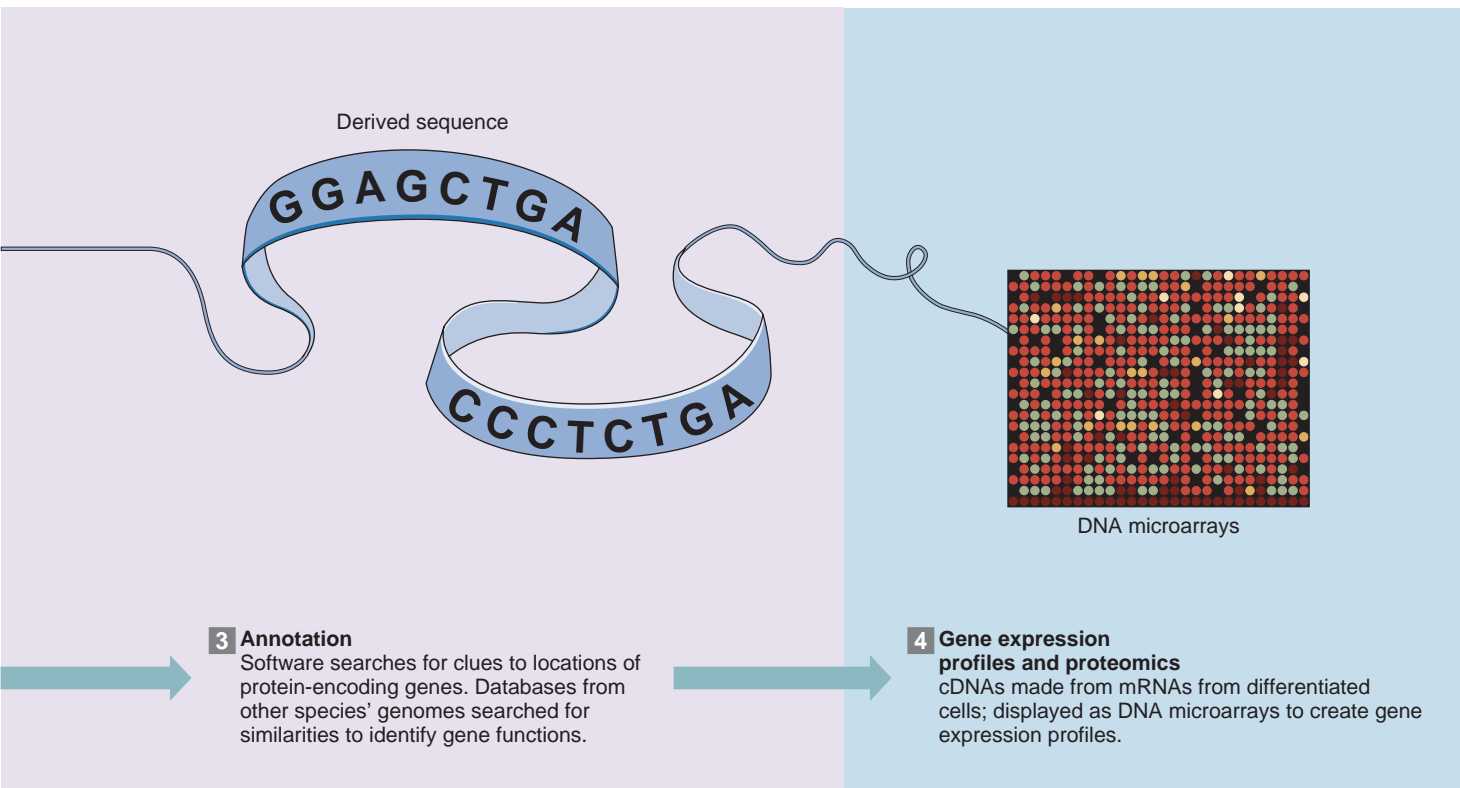
Analysis of one percent of the human genome reveals that:

- Most of the genome is transcribed.
- DNA sequences previously thought not to be transcribed actually are, and some overlap exons.
- The genome has more promoters, and therefore more ways to build genes from its parts, than suspected.
- Control sequences are not only at the starts of genes—they are all over.
- Chromatin structure controls DNA replication as well as transcription.
- 5% of the human genome is highly conserved in all mammals.
- Functional parts of the genome may vary among species. These sequences may represent a DNA store that may serve as “a warehouse for evolution” that may be species-specific.

## 22.3 Comparative Genomics

Hundreds of species have had their genomes sequenced. The first were viruses and bacteria, because genome shotgunning works best on small genomes. Then the genomes of our closest relatives were sequenced—mice, rats, chimps and our favorites, cats and dogs. Most informative, however, have been the genomes of species that represent evolutionary crossroads. These are organisms that introduced a new trait or were the last to have an old one.

In comparing DNA sequences among different modern species, researchers infer evolutionary relationships from DNA sequences that are conserved among species and presumably were selected through time. **Figure 22.7** shows one way of displaying short sequence similarities, called a pictogram. DNA sequences from different species are aligned, and the bases at different points indicated. A large letter A, C, T or G indicates, for example, that all species examined have the same base at that site. A polymorphic site, in contrast, has different bases for different species.



**Figure 22.7 A pictogram indicates conservation of sequence.** Genomes can be compared site by site. These pictograms are for short sequences in corresponding regions of the human, mouse, rat, and chicken genomes. A large letter means that all four species have the same base at that site. If four letters appear in one column, then the species differ. Pictogram (a) is not highly conserved; (b) is.

The field of **comparative genomics** uses conserved sequences to identify biologically important genome regions. However, the ENCODE project indicates

exceptions—conserved sequences with no apparent function. Either we haven't discovered the functions, or genomes include “raw material” for future functions. **Figure 22.8** presents a few organisms whose genomes have been sequenced. Following are examples of the types of information inferred from conserved DNA sequences.

#### The minimum gene set required for life

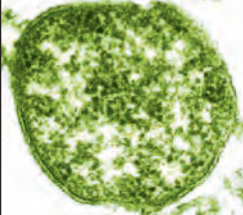

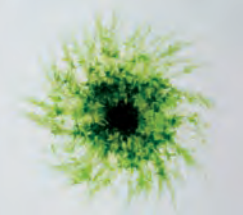






The smallest microorganism known to be able to reproduce is *Mycoplasma genitalium*. It infects cabbage, citrus fruit, corn, broccoli, honeybees, and spiders, and causes respiratory illness in chickens, pigs, cows, and humans. Researchers call its tiny genome the “near-minimal set of genes for independent life.” Of 480 protein-encoding genes, 265 to 350 are essential. Considering how *Mycoplasma* uses its genes reveals the fundamental challenges of being alive.

**Fundamental distinctions among the three domains of life** *Methanococcus jannaschii* is a microorganism that

lives at the bottom of 2,600-meter-tall “white smoker” chimneys in the Pacific Ocean, at high temperature and pressure and without oxygen. As archaea, these cells lack nuclei, yet replicate DNA and synthesize proteins in ways similar to multicellular organisms. The genome sequence confirms that this organism represents a third form of life. Fewer than half of its 1,738 genes had known counterparts among the bacteria, other archaea, or eukaryotes when the genome was sequenced. Even the genome of *E. coli*, the best-studied microorganism, held surprises. The functions of more than a third of *E. coli*'s 4,288 genes remain a mystery.

#### The simplest organism with a nucleus

The paper in *Science* magazine that introduced the genome of the yeast *Saccharomyces cerevisiae* was entitled “Life with 6,000 Genes.” But the unicellular yeast is more complex than this title implies. About a third of its 5,885 genes have counterparts among mammals, including at least 70 implicated in human diseases. Understanding what a gene does in yeast can provide clues to how it affects human health. For example, mutations in counterparts of yeast cell cycle control genes cause cancer in humans.

<b>Bacterium</b> <i>(Dehalococcoides ethenogenes)</i>  ~1.5 million bases		<b>Protozoan</b> <i>(Cryptosporidium parvum)</i>  ~9.1 million bases		<b>Moss</b> <i>(Physcomitrella patens)</i>  ~500 million bases	
<ul style="list-style-type: none"> <li>■ Bioremediation: Dechlorinates water pollutants</li> <li>■ Biotechnology: Transfer 19 dechlorinating enzymes</li> </ul> a.		<ul style="list-style-type: none"> <li>■ Human pathogen: Diarrheal illness, severe in immunosuppressed</li> <li>■ Lacks 2 organelles</li> <li>■ Difficult to culture in lab because of unusual metabolism</li> <li>■ Lives in city water supplies</li> </ul> b.		<ul style="list-style-type: none"> <li>■ Biotechnology: genes provide dehydration resistance. Transfer?</li> <li>■ Genome easy to manipulate</li> <li>■ Evolution: first land plants</li> </ul> c.	
<b>Honey Bee</b> <i>(Apis mellifera)</i>  ~300 million bases		<b>Coelacanth</b> <i>(Latimeria menadoensis)</i>  ~1.7 billion bases		<b>Red jungle fowl</b> <i>(Gallus gallus)</i>  ~1 billion bases	
<ul style="list-style-type: none"> <li>■ Agriculture: honey</li> <li>■ Animal societies</li> <li>■ Compare to other insect genomes</li> <li>■ Ecology: Compare to Africanized bees in southwestern U.S.</li> </ul> d.		<ul style="list-style-type: none"> <li>■ Evolution: "living fossil" unchanged from ancestor that preceded land tetrapods</li> <li>■ Thought extinct until 1938 discovery near South Africa</li> <li>■ Genome easier to study than other fishes because few repeats</li> </ul> e.		<ul style="list-style-type: none"> <li>■ Evolution: Dinosaur descendant; conserved control sequences</li> <li>■ Good model organism. Can study early development in eggs, and aging</li> <li>■ Same number of genes as humans, but genome 1/3 the size</li> <li>■ Agriculture: Identify genes that limit need for drugs in feed</li> <li>■ Medicine: Carries avian flu virus</li> </ul> f.	
<b>Tammar wallaby</b> <i>(Macropus eugenii)</i>  ~3.6 billion bases		<b>Hereford cow</b> <i>(Bos taurus)</i>  ~3 billion bases		<b>Dog</b> <i>(Canis familiaris)</i>  ~2.5 billion bases	
<ul style="list-style-type: none"> <li>■ Evolution: Marsupials (pouched mammals split from placental mammals ~130 millions years ago)</li> <li>■ Perpetually pregnant; give birth on same day each year</li> <li>■ 1 million on Kangaroo Island, Australia</li> </ul> g.		<ul style="list-style-type: none"> <li>■ Medicine: Transmission of prion disorder (BSE)</li> <li>■ Agriculture: Improved meat and milk production; disease prevention</li> <li>■ Study genetic variability in different breeds</li> </ul> h.		<ul style="list-style-type: none"> <li>■ Evolution: Extreme artificial selection created 300+ breeds; compare 10 breeds, wolves, coyote</li> <li>■ 400+ diseases from founder effect and inbreeding</li> <li>■ Medicine: Diseases occur in humans, too (rheumatoid arthritis, cancers, heart and eye disorders, deafness)</li> <li>■ Biotechnology: Pioneered diabetes treatment and bone marrow transplant</li> </ul> i.	

**Figure 22.8** A sampling of genomes, organized according to increasing evolutionary closeness to humans. Listed are some items of interest about each.



## The basic blueprints of an animal

The genome of the tiny, transparent, 959-celled nematode worm *Caenorhabditis elegans* is packed with information on what it takes to be an animal. Thanks to researchers who, in the 1960s, meticulously tracked the movements of each cell as the animal developed, much of the biology of this organism was already known before its 97 million DNA bases were revealed late in 1998. The worm's signal transduction pathways, cytoskeleton, immune system, apoptotic pathways, and even brain proteins are very similar to our own.

The sequencing of the fruit fly (*Drosophila melanogaster*) genome held a big surprise—it has 13,601 genes, fewer than the 18,425 in the much simpler worm. Of 289 disease-causing genes in humans, 177 have counterparts in *Drosophila*. The fly may serve as a model for humans in testing new treatments.

**Life on land** Before 450 million years ago, according to fossil evidence, life was confined to the seas, where it was abundant and diverse. Algae, microorganisms, and jawless fishes shared the depths. The first organisms to colonize land were the mosses, and for this reason, the genome of the modern moss *Physcomitrella patens* (figure 22.8c) was sequenced. Mosses lack stems and leaves and have only a few types of differentiated cells. They dominated landscapes until plants that had seeds and vessels evolved some 200 million years later.

By the time animals ventured onto land, plants had already taken root. Sea residents whose descendants were probably among those first land dwellers were the lobe-finned fishes, which have fleshy, strong fins that could have evolved into the first limbs. Two types of lobe-finned fishes persist today and resemble their fossilized forms—the lungfishes and two species of coelacanths. Because the lungfish genome is huge, researchers analyzed the smaller coelacanth genome (figure 22.8e). The huge fish was thought to be extinct until one was discovered near the coast of South Africa in 1938. Today they live in the Comoro Islands in the Indian Ocean. Information in the coelacanth genome may reveal the traits necessary for the evolution of the tetrapods—vertebrates with four limbs.

**From birds to mammals** The sequencing of the chicken genome (figure 22.8f) marked a number of milestones—the first agricultural animal, the first bird, and, as such, the first direct descendant of dinosaurs. The genome of the red jungle fowl *Gallus gallus* is remarkably like our own, minus many repeats, but its genome organization is intriguing. Like other birds, fishes, and reptiles, but not mammals, the chicken genome is distributed among very large macrochromosomes and tiny microchromosomes. Repeats may have been responsible for the larger sizes of mammalian chromosomes. However, because we do not share as many DNA sequences with the chicken as we do our fur-bearing relatives, those that we do have in common are likely to represent the long-sought control regions of the genome.

**From chimps to humans** Most comparisons of the human genome to those of other species seek similarities. But comparisons of our genome to the genome of the chimpanzee *Pan troglodytes*, our closest relative, aim to find the opposite—genetic differences may refine our knowledge about what makes humans unique, discussed in Reading 16.1. Our genomes differ by 1.2 percent, equaling about 40 million DNA base substitutions. Within those differences may lie the answers to compelling medical questions. Our cancer rates differ; humans are susceptible to malaria, but chimps are not; humans develop Alzheimer disease, and chimps do not; and the course of HIV is deadlier than the chimp version, SIV.

As researchers compare genomes, an international consortium is cataloging species according to selected short genome regions that vary among species but not much within species. The goal is to establish genetic “barcodes” for all species, much as barcodes are used to identify products in a store. Genetic barcodes will have many applications, from energy research, to health and veterinary care to military uses.

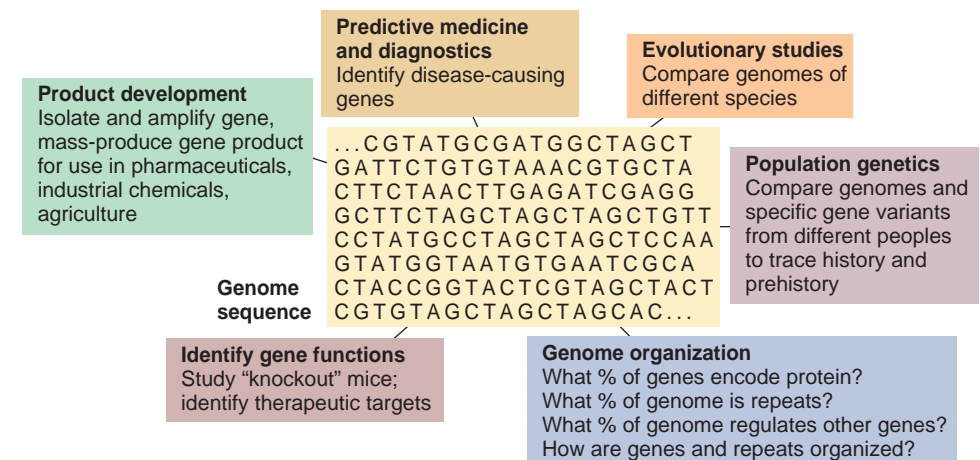
## Key Concepts

1. Comparative genomics seeks conserved sequences among species to infer evolutionary transitions.
2. Comparisons between the chimp and human genomes focus on differences that help to distinguish our species.
3. Species can be distinguished using genetic “barcodes.”

## 22.4 Do You Want Your Genome Sequenced?

With the turn of the century, genetics was catapulted from a somewhat obscure science to an increasingly familiar field with many practical applications, while providing a new view of humanity in the larger context of all life on earth (figure 22.9).

On a personal level, human genome information will focus on the healthy many, rather than the ill few, to better understand



**Figure 22.9** Some applications of human genome information.

disease. For example, researchers are assembling a “healthy cohort”—a group of exceptionally disease-free and vigorous people whose genomes can be searched to reveal shared gene variants that may keep them well. This project is not an attempt to define a “perfect” genetic blueprint, but one that might suggest new types of treatments based on how protective gene variants function and interact. Comparing the lucky healthy cohort to groups of people who have the same disorder will help to pinpoint the basis of their illness.

Another type of study is to scrutinize the genomes of people at high risk for an illness who do not have it. Why does one 40-year, two-pack-a-day smoker *not* develop lung cancer, while another does? Why do only some people who inherit *BRCA1* mutations develop breast cancer?

Identification of disease-causing genes that has proceeded for half a century will continue, but with unprecedented precision. Cancer will no longer be considered “a” disease, but several distinct errors in cell cycling—sharing a phenotype, but not a genotype, and hence requiring different treatments. Each genetically influenced disease in an individual will be considered in the context of the entire genome.

Future treatments based on genome information will not be limited to correcting or circumventing genetic flaws, or supplying missing proteins. Discovering which gene variants contribute to which diseases, and how they do so, will enable us to identify risk factors that are easier to control—those from the environment.

The first two individuals to have their genomes sequenced were Craig Venter and James Watson—genomics celebrities. You

will likely have the opportunity to have your genome sequenced. Should you? To decide, imagine how the information might be used, or misused:

- Health insurance might be based on which disease and susceptibility gene variants you have inherited.
- A diagnosis of cancer, prediction of its course, or determining which treatments will work best, might be done in minutes following a genome scan.
- Gene variants that affect intelligence might be used in college admission decisions or in class placements.
- Gene variants that affect strength and endurance might be considered in tryouts for athletic teams or used to determine whether some competitors have unfair genomic advantages.
- People might consider genome information in choosing partners.

The ability to easily sequence our genomes continues a long-held curiosity about our genetic selves. Since the dawn of humanity, people have probably noted inherited traits, from height and body build, to hair and eye color, to talents, to behavioral quirks, to illnesses. Genetics provides the variety that makes life interesting.

The science of genetics grew out of questions surrounding plant and animal breeding. It became human-oriented in the mid-twentieth century with the recognition that certain characteristics and conditions run in families, sometimes recurring with predictable frequencies. Today, genetics and

genomics are often in the news, and are beginning to impact many areas of health care.

You will likely encounter genetic technologies discussed in this book. In the near future, you might

- be offered a DNA microarray test to diagnose or treat a medical condition.
- serve on a jury and be asked to evaluate DNA profiling evidence.
- take a panel of genetic tests before trying to have a child.
- seek preimplantation genetic diagnosis to ensure that your child does not inherit a particular gene.
- help a parent or other loved one through chemotherapy, with some assurance, thanks to DNA testing, that the most effective drugs will be tried first.
- eat a genetically modified fruit or vegetable (you likely have already done this).
- receive a body part from a pig, with cell surfaces matched to your own.
- take medicine manufactured in a transgenic organism.

The list of applications of genetic technology is long and ever-expanding. I hope that this book has offered you glimpses of the future and prepared you to deal personally with the choices that genetic technology will present to you. Let me know your thoughts!

Ricki Lewis  
ralewis@nycap.rr.com

## Summary

### 22.1 From Genetics To Genomics

1. Genetic maps have increased in detail and resolution, from cytogenetic and linkage maps to physical and sequence maps.
2. Positional cloning discovered individual genes by beginning with a phenotype and gradually identifying a causative gene, localizing it to part of a chromosome.
3. Genomics considers many genes and compares genomes of different species.

### 22.2 The Human Genome Project

4. Automated DNA sequencing and the ability of computers to align and derive long base sequences were vital to sequencing the human genome.
5. In the Sanger method of DNA sequencing, DNA fragments differing in size and with one labeled end base are aligned, and the sequence read off from the end bases.
6. The human genome project began in 1990 under the direction of the DOE and NIH. Technological advances sped the sequencing.
7. Several copies of a genome are cut and the pieces sequenced, overlapped, and aligned to derive the continuous sequence. For the human genome, the International Consortium used a chromosome-by-chromosome approach

and Celera Genomics used whole genome shotgunning.

8. Analysis of a representative one percent of the human genome showed that nearly all DNA is transcribed and that gene function is more complex than was thought.

## 22.3 Comparative Genomics

9. Identifying conserved regions among genomes of different species reveals some genes with vital functions.

10. Distinctions between the chimp and human genome sequences can indicate how we differ from other primates.

## 22.4 Do You Want Your Genome Sequenced?

11. Comparing the genomes of a healthy cohort to groups of people with certain diseases may reveal how gene combinations maintain health. Clues to

health also lie in the genome sequences of people at high risk for certain disorders who do not become ill.

12. Understanding how genes contribute to disease will identify controllable risk factors.

# Review Questions

1. Why was the human genome sequenced?
2. Why is a cytogenetic map less precise than a sequence map?
3. How did family linkage data help in sequencing the human genome?
4. How were researchers wrong to call non-protein-encoding parts of the genome “junk”?
5. In 1966, Francis Crick suggested that knowing the genome of a simple bacterial cell would reveal how life works. What evidence indicates that he was mistaken?
6. Two difficulties in sequencing the human genome were the large number of repeat sequences and the fact that DNA is double-stranded. How did these characteristics complicate sequencing?
7. Why must several copies of a genome be cut up to sequence it?
8. If a researcher wanted to create a genome of a free-living life form, which organism could serve as a model?
9. Many mammalian species have genomes that are about the same size as ours, but have different numbers of genes. How is this possible?
10. Why is it easier to detect conserved DNA sequences that control gene expression by comparing the human genome to a fish genome than to another primate genome?
11. If you knew your genome sequence, what would you do with the information?

# Applied Questions

1. Celera Genomics actually sequenced several different human genomes. Why would the sequences not be identical?
2. Suggest a species you believe should have its genomes sequenced, and what information you think the sequences might reveal.
3. Which criteria do you think should be followed to decide the order in which genomes from different species are sequenced?
4. Restriction enzymes break a sequence of DNA bases into the following pieces:  
T T A A T A T C G  
C G T T A A T A T C G C T A G  
G C T T C G T T  
A A T A T C G C T A G C T G C A  
C T T C G T  
T A G C T G C A  
G T T A A T A T C G C T A G C T G C A  
How long is the original sequence? Reconstruct it.
5. One newly identified human gene has counterparts (homologs) in bacteria, yeast, roundworms, mustard weed, fruit flies, mice, and chimpanzees. A second gene has homologs in fruit flies, mice, and chimpanzees only. What does this information suggest about the functions of these two human genes with respect to each other?
6. Headlines about sequencing genomes of such unusual organisms as sea squirts and pufferfish often serve as material for comedians. Why, scientifically, is it important to sequence the genomes of a variety of organisms?
7. How should we decide who should have their genome sequenced, under what conditions, and who should have access to the resulting information?
8. The “X Prize” program began in the last century to encourage invention in the aerospace industry. In 2006, an X Prize of \$10 million was offered for the invention of a device that can sequence 100 human genomes in under 10 days, for less than \$10,000 per genome and with an error rate of better than one per 10,000 DNA bases.
  - a. How close does 454 sequencing come to meeting the X Prize goal?
  - b. Do you think that a contest is a good way to encourage scientific innovation?
9. When the idea of sequencing the human genome was first discussed, some researchers thought it would be too straightforward and boring, and that amassing large amounts of information was not creative. Discuss one way that genome sequencing has turned out to be more complicated and/or more creative than anticipated.
10. In medical practice, an “incidentaloma” is a test result that a physician wasn’t looking for—such as a tumor on a scan to detect



a broken bone. Soon, it will be possible to scan anyone's genome. Some researchers are concerned that "incidentalomas" will turn up in genome scans—that is, disease-causing genes that are entirely unexpected. This may lead to many more diagnoses than the current health care system can handle. Suggest a way to prepare for dealing with incidentalomas that arise from genome screening. For example, discuss criteria for deciding what to tell a patient and what not to tell.

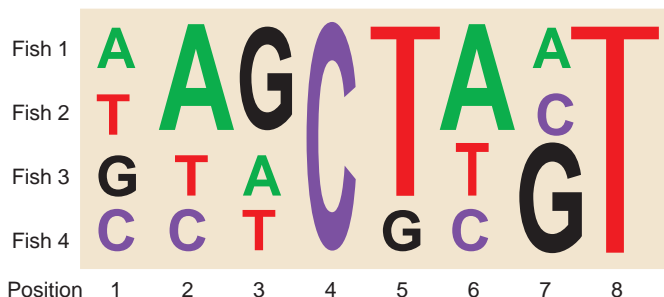
## Web Activities

Visit the ARIS website at [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8). Select **Self Study**, **chapter 22**, and **Web Activities** to find the website links needed to complete the following activities.

11. Go to the ELSI web pages. Discuss one societal concern arising from genomics, and how it might affect you.
12. Go to the website for The Institute For Genomic Research (<http://www.tigr.org/>). List five genomes that are being sequenced and the diseases that they cause in humans.
13. Go to [http://www.ornl.gov/sci/techresources/Human\\_Genome/posters/chromosome/chromo01.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/chromo01.shtml). Select a human chromosome and click on it to see the loci of disease-causing genes. Select three diseases on three chromosomes, and consult OMIM to describe the phenotypes.

## Case Studies

14. After the tsunami that devastated countries bordering the Indian Ocean on December 26, 2004, many organisms never before seen washed up on shore. Researchers collected specimens and sequenced DNA to try to classify the fishes. Consider the following 8-base segment known from cytogenetic analysis to be similar among the species:



- a. Write the sequences for the two most closely related fishes.
- b. Which position(s) in the sequence are highly conserved?
- c. Which position(s) in the sequence are the least conserved?
- d. Which site is probably not essential, and how do you know this?

- e. A coelacanth has C T A C T G G T for this section of the genome. Which of the mystery fishes is the coelacanth's closest relative?
15. The cassava genome project is sequencing the genome of this melon-like crop that feeds one billion people. Understanding how it stores starch can perhaps enable researchers to farm cassava for use as a biofuel. Suggest another plant for which genome sequencing may yield practical applications.

## A Second Look

1. Explain how researchers deduced that 688 genes shared between humans and the alga could include a gene that affects cilia.
2. What are the benefits and limitations of comparing genomes of model organisms, compared to less familiar ones?
3. Explain why cilia genes are expressed in many cell types in many organisms.

Learn to apply the skills of a genetic counselor with these additional cases found in the *Case Workbook in Human Genetics*.

Diffuse large B cell lymphoma  
Muscle cell DNA microarray



**Do you need additional review?** Visit [www.mhhe.com/lewisgenetics8](http://www.mhhe.com/lewisgenetics8) for practice quizzes, animations, videos, and activities designed to help you master the material in this chapter.

# Glossary

Pronunciations are provided for technical terms.

KEY ə = eh

– = long vowel sound

˘ = short vowel sound

ː = heavy accent

ˑ = light accent

^ = aw

## A

**acrocentric chromosome** (ăk'rō sĕn'trĭk krōmə sōm) A chromosome in which the centromere is located near one end.

**adaptive immunity** (ĭ-myōō'nĭ-tē) A slow, specific immune response that develops after exposure to a foreign antigen.

**adenine** (ăd'en-ēn') One of two purine nitrogenous bases in DNA and RNA.

**allele** (ə-lēl') An alternate (variant) form of a gene.

**alternate splicing** Building different proteins by combining exons of a gene in different ways.

**amino** (ə-mē'nō) **acid** A small organic molecule that is a protein building block.

**amniocentesis** (ăm'nē-ō-sĕn-tē'sĭs) A prenatal diagnostic procedure performed on a small sample of amniotic fluid, which contains fetal cells and biochemicals. A chromosome chart is constructed from cultured fetal cells, and tests for inborn errors of metabolism are done on fetal biochemicals.

**anaphase** (ănă-făz') The stage of mitosis when the centromeres of replicated chromosomes part.

**aneuploid** (ăn'yū-ploid') A cell with one or more extra or missing chromosomes.

**angiogenesis** (ăn''je-o-jen'ă-sis) Formation of new blood vessels.

**antibody** (ăn'tē-bōd'ē) A multisubunit protein, produced by B cells, that binds a specific foreign antigen at one end, alerting the immune system or directly destroying the antigen.

**anticodon** (ăntē-kō'dōn) A three-base sequence on one loop of a transfer RNA molecule that is complementary to an mRNA codon, and brings together the appropriate amino acid and its mRNA.

**antigen** (ăn'tē-jən) A molecule that elicits an immune response.

**antigen binding sites** (ăn'tē-jən) Specialized ends of antibody chains.

**antigen** (ăn'tē-jən) **-presenting cell** A cell displaying a foreign antigen.

**antiparallel** The head-to-tail position of the entwined chains of the DNA double helix.

**apoptosis** (ăpō-tō'sĭs) A form of cell death that is a normal part of growth and development.

**assisted reproductive technologies** Procedures that replace a gamete or the uterus to help people with fertility problems have children.

**association study** A case-control study in which genetic variation, often measured as SNPs that form haplotypes, is compared between people with a condition and unaffected individuals.

**autoantibodies** (ô'tō-ăn'tē-bōdēz) Antibodies that attack the body's own cells.

**autoimmunity** (ô'tō-ĭ-myōō'nĭ-tē) An immune attack against one's own body.

**autosomal** (ô'tă-sōmăl) **dominant** The inheritance pattern of one autosomal allele causing a phenotype, which can affect males and females and does not skip generations.

**autosomal** (ô'tă-sōmăl) **recessive** The inheritance pattern of two autosomal alleles causing a phenotype, which can affect males and females and can skip generations.

**autosome** (ô'tă-sōm) A chromosome that does not have a gene that determines sex.

## B

**balanced polymorphism** (pōl'ē-môr'fizəm) Maintenance of a harmful recessive allele in a population because the heterozygote has a reproductive advantage.

**base excision repair** Removal of up to five bases to correct damage due to reactive oxygen species.

**B cell** A type of lymphocyte that secretes antibody proteins in response to nonself antigens displayed on other immune system cells.

**bioethics** A field that addresses personal issues that arise in applying medical technology and information.

**bioremediation** Use of plants or microorganisms to detoxify environmental pollutants.

**biotechnology** The alteration of cells or biochemicals with a specific application.

**blastocyst** (blăs'tō-sĭst') A hollow ball of cells descended from a fertilized ovum.

**blastomere** (blăstō-mēr') A cell of a blastocyst.

## C

**cancer** (kăn'sər) A group of disorders resulting from loss of cell cycle control.

**cancer stem cells** Stem cells that divide and yield cancer cells and abnormal specialized cells.

**carbohydrate** (kar''bo-hĭ'-drăt) An organic compound that consists of carbon, hydrogen, and oxygen in a 1:2:1 ratio. Includes sugars and starches.

**carcinogen** (kar-sĭnă-jən) A substance that causes cancer.

**case-control study** An epidemiological method in which people with a particular condition are compared to individuals as much like them as possible, but without the disease.

**cDNA library** A collection of DNA molecules reverse transcribed from the mRNAs in a particular cell type.

**cell** (sel) The fundamental unit of life.

**cell** (sel) **cycle** A cycle of events describing a cell's preparation for division and division itself.

**cellular adhesion** A precise series of interactions among the proteins that connect cells.

**cellular immune** (ĩ-myōōn') **response** T cells release cytokines to stimulate and coordinate an immune response.

**centriole** (sēn'-trē-ohl) A structure in cells that organizes microtubules into the mitotic spindle.

**centromere** (sēn'-trō-mir) The largest constriction in a chromosome, located at a specific site in each chromosome type.

**chaperone protein** A protein that binds a polypeptide and guides folding.

**chorionic villus** (kōrē-ōn'ik vīl-us) **sampling** (CVS) A prenatal diagnostic technique that analyzes chromosomes in chorionic villus cells, which, like the fetus, descend from the fertilized ovum.

**chromatid** (krō' mǎ-tīd) A single, very long DNA molecule and its associated proteins, forming half of a replicated chromosome.

**chromatin** (krō' mǎ-tīn) DNA and its associated histone proteins.

**chromatin** (krō' mǎ-tīn) **remodeling** Adding or removing chemical groups to or from histones, which can alter gene expression.

**chromosome** (krō' mǎ-sōm') A structure in a cell's nucleus that carries genes. A chromosome is a continuous molecule of DNA and proteins wrapped around it.

**cleavage** (klēvj) A series of rapid mitotic cell divisions after fertilization.

**clines** (klīnz) Allele frequencies that change from one geographical area to another.

**cloning vector** A piece of DNA used to transfer DNA from a cell of one organism into the cell of another.

**coding strand** The side of the DNA double helix for a particular gene from which RNA is not transcribed.

**codominant** A heterozygote in which both alleles are fully expressed.

**codon** (kō'dōn) A continuous triplet of mRNA that specifies a particular amino acid.

**coefficient of relatedness** The proportion of genes that two people related in a certain way share.

**collectins** (ko-lek'tinz) Immune system molecules that detect viruses, bacteria, and yeasts.

**comparative genomics** (jǎ-nō'mīks) Identifying conserved DNA sequences among genomes of different species.

**comparative genomic hybridization** (CGH) A technique using fluorescent labels to detect copy number differences at specific parts of a genome.

**complement** Plasma proteins that have a variety of immune functions.

**complementary base pairs** The pairs of DNA bases that hydrogen bond; adenine bonds to thymine and guanine to cytosine.

**complementary DNA** (cDNA) A DNA molecule that is the complement of an mRNA, copied using reverse transcriptase.

**concordance** (kǎn-kōr'dens) A measure indicating the degree to which a trait is inherited; percentage of twin pairs in which both members express a trait.

**conditional mutation** (myōō-tǎ'shǎn) A genotype that is expressed only under certain environmental conditions.

**conformation** The three-dimensional shape of a molecule.

**consanguinity** (kōnsǎn-gwīn'ī-tē) Blood relatives having children together.

**copy number variant** A DNA sequence present in different numbers of copies in different individuals; repeats.

**critical period** The time during prenatal development when a structure is sensitive to damage from a mutation or an environmental intervention.

**crossing over** An event during prophase I when homologs exchange parts.

**cytogenetics** (sītō-jǎ-nēt'īks) A discipline that matches phenotypes to detectable chromosomal abnormalities.

**cytokine** (sītō-kīn') A biochemical that a T cell secretes that controls immune function.

**cytokinesis** (sī-tō-kin-ē'-sis) Division of the cytoplasm and its contents.

**cytoplasm** (sī'-tō-plāzm) Cellular contents other than organelles.

**cytosine** (sī'-tō-sēn) One of the two pyrimidine nitrogenous bases in DNA and RNA.

**cytoskeleton** (sī-tō-skēl'ī-tn) A framework of protein tubules and rods that supports the cell and gives it a distinctive form.

## D

**dedifferentiated** A cell less specialized than the cell it descends from. A characteristic of a cancer cell.

**deletion mutation** (myōō-tǎ'-shǎn) A missing sequence of DNA or part of a chromosome.

**deoxyribonucleic** (dē-ōksē-rībō-nōō-klā'ik) **acid** (DNA) The genetic material; the biochemical that forms genes.

**deoxyribose** (dē-ōksē-rī'bōs') 5-carbon sugar in a DNA nucleotide.

**differentiation** Cell specialization, reflecting differential gene expression.

**dihybrid cross** Breeding individuals heterozygous for two traits.

**diploid** (dīp' loid) A cell containing two sets of chromosomes.

**dizygotic** (dīzī-gōt'ik) **(DZ) twins** Twins that originate as two fertilized ova.

**DNA** See **deoxyribonucleic acid**.

**DNA damage response** DNA repair.

**DNA microarray** See **microarray**.

**DNA polymerase** (pǎ-lim'ǎr-ās) (DNAP) An enzyme that adds new bases to replicating DNA and corrects mismatched base pairs.

**DNA probe** A labeled short sequence of DNA that binds its complement in a biological sample.

**DNA profiling** A biotechnology that detects differences in the number of copies of certain DNA repeats among individuals. Used to rule out or establish identity.

**DNA replication** Construction of a new DNA double helix using the information in parental strands as a template.

**dominant** A gene variant expressed when present in one copy.

**duplication** An extra copy of a DNA sequence, usually caused by misaligned pairing in meiosis.

## E

**ectoderm** (ēktō-dūrm) The outermost primary germ layer.

**embryo** (ēm'brē-ō') In humans, prenatal development until the end of the eighth week. Embryo cells can be distinguished from each other, but all basic structures are not yet present.

**embryonic** (ēmbrē-ōn'ik) **stem (ES) cell** A cell that can give rise to all differentiated cell types.

**empiric risk** Probability that a trait will recur based upon its incidence in a population.



**endoderm** (ĕn'dō-dŭrm) The innermost primary germ layer of the primordial embryo.

**endoplasmic reticulum** (ĕndō-plāzmĭk rə-tĭk'ŭ-ləm) (ER) A labyrinth of membranous tubules on which proteins, lipids, and sugars are synthesized.

**enzyme** (ĕnzĭm) A type of protein that speeds the rate of a specific biochemical reaction.

**epigenetic** (ĕpĕ-jə-nĕt'ĭk) A layer of information placed on a gene that is a modification other than a change in DNA sequence, such as methylation.

**epistasis** (ĕpĕ-stā-sis) A gene masking the expression of another.

**epitope** (ep'ĭ-tōp) Part of an antigen that an antibody binds.

**equational division** The second meiotic division, producing four cells from two.

**euchromatin** (yōō-krō'mā-tĭn') Parts of chromosomes that do not stain and that contain active genes.

**eugenics** (yōō-jĕn'ĭks) The control of individual reproductive choices to achieve a societal goal.

**eukaryotic cell** (yōō-kar'ē-ōt'ĭk sel) A complex cell containing organelles, including a nucleus.

**euploid** (yōō'-plōid) A somatic cell with the normal number of chromosomes for the species.

**excision repair** Enzyme-catalyzed removal of pyrimidine dimers in DNA.

**exon** (x-on) Part of a gene that encodes amino acids.

**expressivity** Degree of severity of a phenotype.

## F

**fetus** (fē'təs) The prenatal human after the eighth week of development, when structures grow and specialize.

**founder effect** A type of genetic drift in which a few individuals found a new settlement, perpetuating a subset of alleles from the original population.

**frameshift mutation** (myōō-tā'shən) A mutation that alters a gene's reading frame.

**fusion protein** A protein that forms from translation of transcripts from two genes.

## G

**G<sub>0</sub>** An offshoot of the cell cycle in which the cell remains specialized but does not replicate its DNA or divide.

**G<sub>1</sub>** The stage of the cell cycle following mitosis in which the cell resumes synthesis of proteins, lipids, and carbohydrates.

**G<sub>2</sub>** The stage of the cell cycle following S phase but before mitosis, when certain proteins are synthesized.

**gamete** (gām'ēt) A sex cell.

**gamete intrafallopian transfer** (gām'ēt ĭntrə-fə-lōpĕ-ən) (GIFT) An infertility treatment in which sperm and oocytes are placed in a woman's uterine tube.

**gastrula** (gāstrə-lə) A three-layered embryo.

**gene** (jĕn) A sequence of DNA that instructs a cell to produce a particular protein.

**gene** (jĕn) **expression** (jĕn) Transcription of a gene.

**gene** (jĕn) **expression profiling** (jĕn) Use of DNA microarrays to detect the types and amounts of cDNAs reverse transcribed from the mRNAs in a particular cell source.

**gene** (jĕn) **pool** (jĕn) All the genes in a population.

**gene** (jĕn) **therapy** Replacing a malfunctioning gene to alleviate symptoms.

**genetic** (jə-nĕt'ĭk) **code** The correspondence between specific RNA triplets and the amino acids they specify.

**genetic** (jə-nĕt'ĭk) **counselor** A medical specialist who calculates risk of recurrence of inherited disorders in families, applying the laws of inheritance to pedigrees.

**genetic determinism** (jə-nĕt'ĭk) The conclusion that a characteristic is inevitable because it has an inherited component.

**genetic** (jə-nĕt'ĭk) **drift** Changes in gene frequencies in small groups reproductively separated from a larger population.

**genetic** (jə-nĕt'ĭk) **heterogeneity** A phenotype that can be caused by variants of any of several genes.

**genetic** (jə-nĕt'ĭk) **load** The collection of deleterious recessive alleles in a population.

**genetics** (jə-nĕt'ĭks) The study of inherited variation.

**genome** (jĕ'nōm) The complete set of genetic instructions in the cells of a particular type of organism.

**genomic** (jĕ nō'm ĭk) **imprinting** Differing of the phenotype depending upon which parent transmits a particular allele.

**genomic** (jĕ nōm ĭk) **library** A collection of DNA pieces representing the genome of an individual, including introns.

**genomics** (jĕ nōm ĭks) The study of the functions and interactions of many genes, or comparing genomes.

**genotype** (jĕ n'ə- tĭp) The allele combinations in an individual that cause particular traits or disorders.

**genotypic** (jĕn'ə- tĭp'ĭk) **ratio** The ratio of genotype classes expected in the progeny of a particular cross.

**germline gene therapy** Genetic alterations of gametes or fertilized ova, which perpetuate the change throughout the organism and transmit it to future generations.

**germline mutation** A mutation in every cell in an individual.

**Golgi** (gōl'jĕ) **apparatus** An organelle, consisting of flattened, membranous sacs, that packages secretion components.

**gonads** (gō'-nadz) Paired structures in the reproductive system where sperm or oocytes are manufactured.

**growth factor** A protein that stimulates mitosis.

**guanine** (gwa' nĕn) One of the two purine nitrogenous bases in DNA and RNA.

## H

**haploid** (hăp' loid) A cell with one set of chromosomes.

**haplotype** (hăp' lō tĭp) A series of known DNA sequences or single nucleotide polymorphisms linked on a chromosome.

**Hardy-Weinberg equilibrium** An idealized state in which gene frequencies in a population do not change from generation to generation.

**heavy chains** The two longer polypeptide chains of an antibody subunit.

**hemizygous** (hĕm' ē-zĭ' gəs) The sex that has half as many X-linked genes as the other; a human male.

**heritability** An estimate of the proportion of phenotypic variation in a group due to genes.

**heterochromatin** (hĕtə-rō-krō'mătĭn) Dark-staining chromosome parts that have few protein-encoding genes.

**heterogametic** (hĕt'ə-rō-gə-mĕ'tĭk) **sex** The sex with two different sex chromosomes; a human male.

**heteroplasmy** (hĕt'ə-rō-plāz-mĕ) Mitochondria in the same cell having different alleles of a particular gene.

**heterozygous** (hĕtə-rō-zĭ'gəs) Having two different alleles of a gene.

**histone** (hĭs'tōn) A type of protein around which DNA entwines.

**hominins** (hŏm'ə-nĭnz) Animals ancestral to humans only.

**hominoids** (hŏmə-noidz) Animals ancestral to apes and humans only.

**homogametic** (hŏmō-gə-mĕ'tĭk) **sex** The sex with identical types of sex chromosomes; the human female.

**homologous** (hō-mŏl'ə-gəs) **pairs** Chromosomes with the same gene sequence.

**homozygous** (hŏmō-zĭ' gəs) Having two identical alleles of a gene.

**human leukocyte antigen** (lōōkə-sĭt' ən'tĭ-jən) (HLA) **complex** Genes closely linked on the short arm of chromosome 6 that encode cell surface proteins important in immune system function.

**humoral** (yŏō' mər-əl) **immune response** Process in which B cells secrete antibodies into the bloodstream.

## I

**idiotype** (id'ē-o-tĭp) Part of an antibody molecule that binds an antigen.

**incidence** The number of new cases of a disease during a certain time in a particular population.

**incomplete dominance** A heterozygote intermediate in phenotype between either homozygote.

**independent assortment** The random arrangement of homologous chromosome pairs, in terms of maternal or paternal origin, down the center of a cell in metaphase I. Inheritance of a gene on one chromosome does not influence inheritance of a gene on a different chromosome. (Mendel's second law)

**infertility** The inability to conceive a child after a year of unprotected intercourse.

**inflammation** Part of the innate immune response that causes an infected or injured area to swell with fluid, turn red, and attract phagocytes.

**innate immunity** (ĭ-myŏō'nĭ-tē) Components of immune response that are present at birth and do not require exposure to an environmental stimulus.

**inner cell mass** A clump of cells on the inside of the blastocyst that will continue developing into an embryo.

**insertional translocation** A rare type of translocation in which a part of one chromosome is part of a nonhomologous chromosome.

**insertion mutation** (myŏō-tā'-shən) A mutation that adds DNA bases.

**interferon** (in'tər-fēr'on) A type of cytokine.

**interleukin** (in'tər-loo'kin) A type of cytokine.

**intermediate filament** A type of cytoskeletal component made of different proteins in different cell types.

**interphase** (ĭn'tər-fāz') Stage when a cell is not dividing.

**intracytoplasmic** (ĭn'trə-sĭtō-plāzmĭk) **sperm injection** (ICSI) Injection of a sperm cell nucleus into an oocyte, to overcome lack of sperm motility.

**intrauterine** (ĭn'trə-yŏō'tər-ĭn) **insemination** An infertility treatment in which donor sperm are placed in the cervix or uterus.

**intron** (ĭn trŏn) Part of a gene that is transcribed but is excised from the mRNA before translation into protein.

**in vitro** (ĭn vē'trŏ) **fertilization** (IVF) Placing oocytes and sperm in a laboratory dish with appropriate biochemicals so that fertilization occurs, then, after a few cell divisions, transferring the embryos to a woman's uterus.

**in vivo gene therapy** Direct genetic manipulation of cells in the body.

## K

**karyotype** (kă'rĕ-ŏ-tĭp) A size-order chromosome chart.

## L

**law of independent assortment** See **independent assortment**.

**law of segregation** See **segregation**.

**lethal allele** (ə-lĕl') An allele that causes death before reproductive maturity or halts prenatal development.

**ligand** (lĭ'gənd) A molecule that binds to a receptor.

**ligase** (lĭ'gās) An enzyme that catalyzes the formation of covalent bonds in the sugar-phosphate backbone of a nucleic acid.

**light chains** The two shorter polypeptide chains of an antibody subunit.

**linkage** Genes on the same chromosome.

**linkage disequilibrium** Extremely tight linkage between DNA sequences.

**linkage maps** Maps that show gene order on chromosomes, determined from crossover frequencies between pairs of genes.

**lipid** (lĭpĭd) A type of organic molecule that has more carbon and hydrogen atoms than oxygen atoms. Includes fats and oils.

**lysosome** (lĭ'sŏ-sŏm) A saclike organelle containing enzymes that degrade debris.

## M

**macroevolution** (măk'rŏ-ĕv'ə-lŏŏshən) Genetic change sufficient to form a new species.

**major histocompatibility** (hĭstŏ-kəm-pătə-bĭlĭ-tē) **complex** (MHC) A gene cluster, on chromosome 6 in humans, that includes many genes that encode components of the immune system.

**manifesting heterozygote** (hĕt'ə-rŏ-zĭgŏt) A female carrier of an X-linked recessive gene who expresses the phenotype because the normal allele is inactivated in some tissues.

**meiosis** (mĭ-ŏ'sĭs) Cell division that halves the number of chromosomes to form haploid gametes.

**mesoderm** (mĕz-ŏ-dŭrm) The middle primary germ layer.

**messenger RNA** (mRNA) A molecule of RNA complementary in sequence to the template strand of a gene that specifies a protein product.

**metacentric chromosome** (mĕtə-sĕn'trĭk krŏmŏ-sŏm) A chromosome with the centromere approximately in the center.

**metaphase** (mĕtə-fāz) The stage of mitosis when chromosomes align along the center of the cell.

**metastasis** (mĕtə-stā'-sĭs) Spread of cancer from its site of origin to other parts of the body.

**microarray** A set of target genes embedded in a glass chip, to which labeled cDNAs from a sample bind and fluoresce. Microarrays show patterns of gene expression.

**microevolution** Change of allele frequency in a population.

**microfilament** A solid rod of actin protein that forms part of the cytoskeleton.

**microtubule** (mīkrō-tōōbyōōl) A hollow structure built of tubulin protein that forms part of the cytoskeleton.

**mismatch repair** Proofreading of DNA for misalignment of short, repeated segments.

**missense** (mīś'sēns) A single base change mutation that alters an amino acid.

**mitochondrion** (mītō-kōn'drē-ən) An organelle consisting of a double membrane that houses enzymes that catalyze reactions that extract energy from nutrients.

**mitosis** (mī-tōsīs) Division of somatic (non-sex) cells.

**mode of inheritance** The pattern in which a gene variant passes from generation to generation, dominant or recessive, autosomal or sex-linked.

**molecular evolution** Changes in protein and DNA sequences over time used to estimate how recently species diverged from a common ancestor.

**monoclonal** (mōnə-klō'nəl) **antibody** (MAB) A single antibody type, produced from a B cell fused to a cancer cell (a hybridoma).

**monohybrid** (mōn'ō-hībrīd) **cross** A cross of two individuals who are heterozygous for a single trait.

**monosomy** (mōn'ō-sō'mē) A human cell with 45 (one missing) chromosomes.

**monozygotic** (mōnō-zī-gōt'īk) (MZ) **twins** Twins that originate as a single fertilized ovum; identical twins.

**morula** (mōr' yə-lə) The very early prenatal stage that resembles a mulberry.

**multifactorial trait** A trait or illness determined by several genes and the environment.

**multiregional hypothesis** The idea that the traits of humanity originated in several places about 200,000 years ago.

**mutagen** (myōō'tə-jən) A substance that changes, adds, or deletes a DNA base.

**mutant** (myōō'tnt) An allele that differs from the normal or most common allele, altering the phenotype.

**mutation** (myōō-tā'shən) A change in a protein-encoding gene that affects the phenotype and affects less than one percent of a population.

## N

**natural selection** Differential survival and reproduction of individuals with particular phenotypes in particular environments, which may alter allele frequencies in subsequent generations.

**neural** (nōōr'əl) **tube** A structure in the embryo that develops into the brain and spinal cord.

**nitrogenous** (nī-trōj'ə-nəs) **base** A nitrogen-containing base that is part of a nucleotide.

**nondisjunction** (nōndīs-jūngk'shən) The unequal partitioning of chromosomes into gametes during meiosis.

**nonsense mutation** (myōōtā'shən) A point mutation that changes an amino-acid-coding codon into a stop codon, prematurely terminating synthesis of the encoded protein.

**nonsynonymous codon** (kō'don) A codon that encodes a different amino acid from another codon.

**nucleic** (nōō-klē'ik) **acid** DNA or RNA.

**nucleolus** (nōō-klē'ə-ləs) A structure within the nucleus where ribosomes are assembled from ribosomal RNA and protein.

**nucleosome** (nōō'-klē-ō-sōm) A unit of chromatin structure.

**nucleotide** (nōō-klē-ō-tīd) The building block of a nucleic acid, consisting of a phosphate group, a nitrogenous base, and a 5-carbon sugar.

**nucleotide** (nōō-klē-ō-tīd) **excision repair** Replacement of up to 30 nucleotides to correct DNA damage of several types.

**nucleus** (nōō-klē-əs) A large, membrane-bounded region of a eukaryotic cell that houses DNA.

## O

**oncogene** (ōn'kə-jēn) A gene that normally controls the cell cycle, but causes cancer when overexpressed.

**oocyte** (ō'ə-sīt) The female gamete (sex cell).

**oogenesis** (ōə-jēn'ī-sīs) Oocyte development.

**organelle** (ōr'gə-nēl') A specialized structure in a eukaryotic cell that carries out a specific function.

**ovaries** (ō'və-rēz) The female gonads.

## P

**paracentric** (para sēn'-trīk) **inversion** An inverted chromosome that does not include the centromere.

**pedigree** A chart consisting of symbols connected by lines that depict the genetic relationships and transmission of inherited traits in related individuals.

**penetrance** Percentage of individuals with a genotype who have an associated phenotype.

**pericentric** (pər-ē sēn-trīk) **inversion** An inverted chromosome that includes the centromere.

**peroxisome** (pə-rōk'sī-sōm) An organelle consisting of a double membrane that houses enzymes with various functions.

**phenocopy** (fē' nō-kōp'ē) An environmentally caused trait that occurs in a familial pattern, mimicking inheritance.

**phenotype** (fē' nō-tīp) The expression of a gene in traits or symptoms.

**plasma membrane** (plāz'mə mēm'brān) The selective barrier around a cell, consisting of proteins, glycolipids, glycoproteins, and lipid rafts on or in a phospholipid bilayer.

**plasmid** (plāz' mīd) A small circle of double-stranded DNA found in some bacteria. Used as a vector in recombinant DNA technology.

**pleiotropic** (plēō-trōp'ik) A single-gene disorder with several symptoms. Different symptom subsets may occur in different individuals.

**point mutation** (myōō-tā' shən) A single base change in DNA.

**polar body** A product of female meiosis that contains little cytoplasm and does not continue to develop into an oocyte.

**polar body biopsy** (bī'ōp sē) A genetic test performed on a polar body to infer the genotype of the attached oocyte.

**polygenic** (pōlē-jēn' īk) **traits** Traits determined by more than one gene.

**polymerase** (pōlə'-mə-rās) **chain reaction** (PCR) A nucleic acid amplification technique in which a DNA sequence is replicated in a test tube to rapidly produce many copies.



**polymorphism** (pōlē-mōr' fīz əm) A DNA base or sequence at a certain chromosomal locus that varies in at least 1 percent of individuals in a population.

**polyploid** (pōl'ē-ploid) A cell with one or more extra sets of chromosomes.

**population** A group of interbreeding individuals.

**population bottleneck** Decrease in allele diversity resulting from an event that kills many members of a population, followed by restoration of population numbers.

**population genetics** (jə-nē'tīks) The study of allele frequencies in different groups of individuals.

**population study** Comparison of disease incidence in different groups of people.

**preimplantation genetic (jə-nē'tīk) diagnosis** (PGD) Removing a cell from an 8-celled embryo and testing it for a mutation to deduce the genotype of the embryo.

**prevalence** The number of cases of a disease in a population at a particular time.

**primary germ layers** The three layers of an embryo.

**primary (1°) structure** The amino acid sequence of a protein.

**progenitor cell** A cell whose descendants can follow any of several developmental pathways.

**prokaryotic cell** (prō-kāre-ō'tīk sēl) A cell that does not have a nucleus or other organelles. One of the three domains of life. Bacteria.

**promoter** A control sequence near the start of a gene.

**pronuclei** (prō-nōō'klēī) DNA packets in the fertilized ovum.

**prophase** (prō'fāz) The first stage of mitosis or meiosis, when chromatin condenses.

**prospective study** A study that follows two or more groups.

**proteasome** (prō-tē-ə-sōm) A multiprotein structure in a cell shaped like a barrel through which misfolded proteins pass and are refolded or dismantled.

**protein** A type of macromolecule that is the direct product of genetic information; a chain of amino acids.

**proteome** (prō'tē-ōm) The set of proteins a cell produces.

**proteomics** (prōtē-ō' mīks) Study of the proteins produced in a particular cell type under particular conditions.

**proto-oncogene** (prōtō-ōn'kə-jēn) A gene that normally controls the cell cycle. When overexpressed, it functions as an oncogene, causing cancer.

**pseudoautosomal** (sōō-dō ōtə-sōm'ōl) **region** Genes on the tips of the Y chromosome that have counterparts on the X chromosome.

**pseudogene** (sōō' dō jēn) A gene that does not encode protein, but whose sequence very closely resembles that of a coding gene.

**Punnett square** A diagram used to follow parental gene contributions to offspring.

**purine** (pyōō r'ēn) A DNA base with a two-ring structure; adenine and guanine are purines.

**pyrimidine** (pī-rīm'ī-dēn) A DNA base with a single-ring structure; cytosine, thymine, and uracil are pyrimidines.

## Q

**quantitative trait loci** Genes that determine polygenic traits.

**quaternary (4°) structure** A protein that has more than one polypeptide subunit.

## R

**reading frame** The grouping of DNA base triplets encoding an amino acid sequence.

**receptor** A structure on a cell that binds a specific molecule.

**recessive** An allele whose expression is masked by another allele.

**reciprocal translocation** A chromosome aberration in which two nonhomologous chromosomes exchange parts, conserving genetic balance but rearranging genes.

**recombinant** (rē-kōm'bə-nənt) A series of alleles on a chromosome that differs from the series of either parent.

**recombinant** (rē-kōm'bə-nənt) **DNA technology** Transferring genes between species.

**reduction division** The first meiotic division, which halves the chromosome number.

**replacement hypothesis** The idea that *Homo sapiens* evolved from a *Homo erectus* population in Africa about 200,000 years ago.

**replication fork** Locally opened portion of a replicating DNA double helix.

**ribonucleic acid** (RNA) (rī bō-nōō-klē'īk) A nucleic acid whose bases are A, C, U, and G.

**ribose** (rī'bōs) A 5-carbon sugar in RNA.

**ribosomal** (rī'bōs-ō'məl) **RNA** (rRNA) RNA that, with proteins, comprises ribosomes.

**ribosome** (rī'bō sōm) An organelle consisting of RNA and protein that is a scaffold for protein synthesis.

**risk factor** A characteristic or experience associated with increased likelihood of developing a particular medical condition.

**RNA interference** A natural process that destroys specific mRNA molecules using small interfering RNAs that result from transcribing short sequences on both DNA strands.

**RNA polymerase** (RNAP) (pōl'ə-mə-rās) An enzyme that adds RNA nucleotides to a growing RNA chain.

**Robertsonian** (Rāb-ərt - sō'-nē-ən) **translocation** A chromosome aberration in which two short arms of nonhomologous chromosomes break and the long arms fuse, forming one unusual, large chromosome.

## S

**S phase** The stage of interphase when DNA replicates.

**secondary (2°) structure** Folds in a polypeptide caused by attractions between amino acids close together in the primary structure.

**segregation** The distribution of alleles of a gene into separate gametes during meiosis. (Mendel's first law).

**self-renewal** Defining property of a stem cell; the ability to yield a daughter cell like itself.

**semiconservative replication** DNA synthesis along each half of the double helix.

**sex chromosome** (krō'mə-sōm) A chromosome containing genes that specify sex.

**sex-influenced trait** Phenotype caused when an allele is recessive in one sex but dominant in the other.

**sex-limited trait** A trait that affects a structure or function present in only one sex.

**sex ratio** Number of males divided by number of females multiplied by 1,000 for people of a certain age in a population.

**short tandem repeats** (STRs) Repeats of 2 to 10 DNA bases that are compared in DNA profiling.

**signal transduction** A series of biochemical reactions and interactions that pass information from outside a cell to inside, triggering a response.

**single nucleotide polymorphism** (nōōklēō-tīd pōlē-mōr' fīz'əm) (SNP) Single base sites that differ among individuals. A SNP is present in at least 1 percent of a population.

**somatic cell** (sō-māt'īk sēl) A nonsex cell, with 23 pairs of chromosomes in humans.

**somatic (sō-māt'īk) cell nuclear transfer** Transfer of a somatic cell's nucleus to an enucleated egg, and growth to the 8-cell or blastocyst stage to obtain inner cell mass cells, which are cultured to yield embryonic stem (ES) cells. Given appropriate stimulation, the ES cells divide to produce needed cells.

**somatic (sō-māt'īk) gene therapy** Genetic alteration of a specific cell type, not transmitted to future generations.

**somatic mutation** (sō-māt'īk myōō-tā'shən) A genetic change in a nonsex cell.

**spermatogenesis** (spər-māt'ə-jən'ī-sis) Sperm cell differentiation.

**spermatogonium** (spər'mah-to-gō'ne-um) An undifferentiated cell in a seminiferous tubule that can give rise to a sperm cell in meiosis.

**spermatozoon** (spər-māt'ə-zō'ōn) (sperm) A mature male reproductive cell (meiotic product).

**spindle** A structure composed of microtubules that pulls sets of chromosomes apart in a dividing cell.

**spontaneous mutation** (myōō-tā'sheən) A genetic change that results from mispairing when the replication machinery encounters a base in its rare tautomeric form.

**SRY gene** The sex-determining region of the Y. If the SRY gene is activated, the gonad develops into a testis; if not, an ovary forms under direction of other genes.

**stem cells** Cells that give rise to other stem cells, as well as to cells that differentiate.

**submetacentric chromosome** (süb mēt-ə-sēn'trik krō'mə-sōm) A chromosome in which the centromere establishes a long arm and a short arm.

**sugar-phosphate backbone** The "rails" of a DNA double helix, consisting of alternating deoxyribose and phosphate groups, oriented opposite one another.

**synonymous codons** (kō d ōnz) DNA triplets that specify the same amino acid.

**synteny** (sīn'tə-nē) Correspondence of genes on the same chromosome in several species.

## T

**tandem duplication** A duplicated DNA sequence next to the original sequence.

**T cell** A type of lymphocyte that produces cytokines and coordinates the immune response.

**telomerase** (tə-lōm'ə-rās) An enzyme, including a sequence of RNA, that adds DNA to chromosome tips.

**telomere** (tēl'ə-mīr) A chromosome tip.

**telophase** (tēl'ə-fāz) The stage of mitosis or meiosis when daughter cells separate.

**template strand** The DNA strand carrying the information to be transcribed.

**teratogen** (tə-rāt'ə-jən) A substance that causes a birth defect.

**tertiary (3°) structure** Folds in a polypeptide caused by interactions between amino acids and water. This draws together amino acids that are far apart in the primary structure.

**testes** (tes'tēz) The male gonads.

**thymine** (thī'mēn) One of the two pyrimidine bases in DNA.

**transcription** Manufacturing RNA from DNA.

**transcription factor** A protein that activates the transcription of certain genes.

**transfer RNA** (tRNA) A type of RNA that connects mRNA to amino acids during protein synthesis.

**transgenic organism** (trāns-jen'īk) An individual with a genetic modification in every cell.

**transition** A point mutation altering a purine to a purine or a pyrimidine to a pyrimidine.

**translation** Assembly of an amino acid chain according to the sequence of base triplets in a molecule of mRNA.

**translocation** Exchange between nonhomologous chromosomes.

**translocation carrier** An individual with exchanged chromosomes but no signs or symptoms. The person has the usual amount of genetic material, but it is rearranged.

**transposon** (trāns-pōzōn) A gene or DNA segment that moves to another chromosome.

**transversion** A point mutation altering a purine to a pyrimidine or vice versa.

**trisomy** (trī sō'mē) A human cell with 47 chromosomes (one extra).

**tumor suppressor gene** (tōōmər səprēs'ər jēn) A recessive gene whose normal function is to limit the number of divisions a cell undergoes.

## U

**uniparental disomy** (yū-ni-pə'rent-əl dī sō mē) Inheriting two copies of the same gene from one parent.

**uracil** (yōōr'ə-sīl) One of the four types of bases in RNA; a pyrimidine.

## V

**vaccine** (vak-sē'n) An inactive or partial form of a pathogen that stimulates antibody production.

**variable number of tandem repeats** (VNTRs) Repeats of 10 to 80 DNA bases that are compared in DNA profiles.

**vesicles** (ves-ə-kulz) Bubble-like membrane-bounded organelles that participate in secretion.

**virus** (vī rəs) An infectious particle built of nucleic acid in a protein coat.

## W

**wild type** The most common phenotype in a population for a particular gene.

## X

**X inactivation** The inactivation of one X chromosome in each cell of a female mammal, occurring early in embryonic development.

**X-linked** Genes on an X chromosome.

**X-Y homologs** (hōm'ə-lōgz) Y-linked genes that are similar to genes on the X chromosome.

## Y

**Y-linked** Genes on a Y chromosome.

## Z

**zygote** (zī'gōt) A prenatal human from the fertilized ovum stage until formation of the primordial embryo, at about two weeks.

**zygote intrafallopian transfer** (zī' gōt īn'trə-fə-lō' pē-ən) (ZIFT) An assisted reproductive technology in which an ovum fertilized *in vitro* is placed in a woman's uterine tube.





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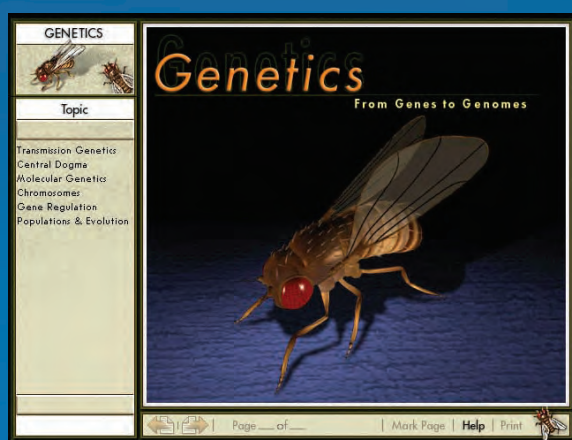
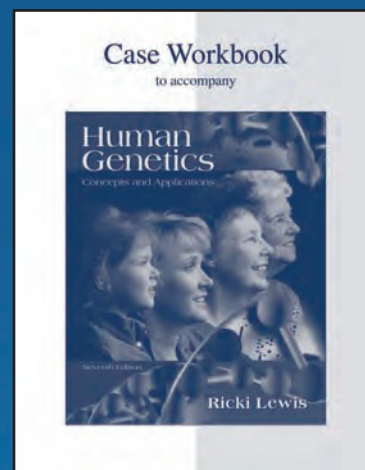
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